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DISEASES OF CHILDREN

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Tuberculin Reactors Among Children in Highly Infected Chicago Areas
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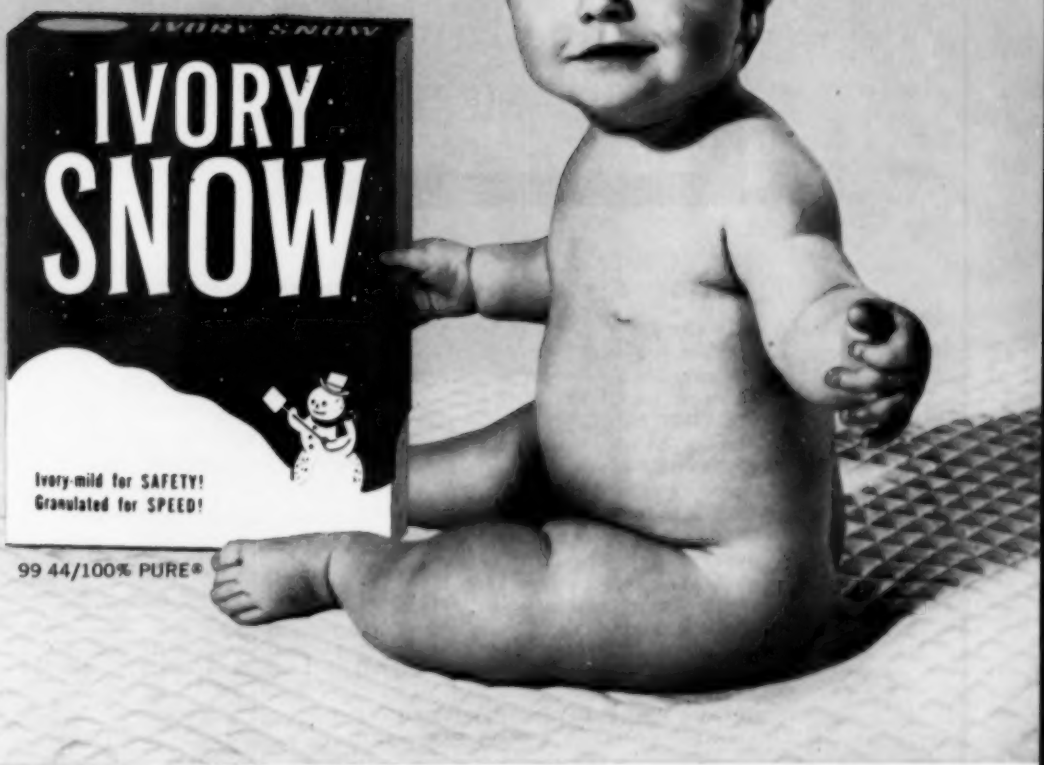

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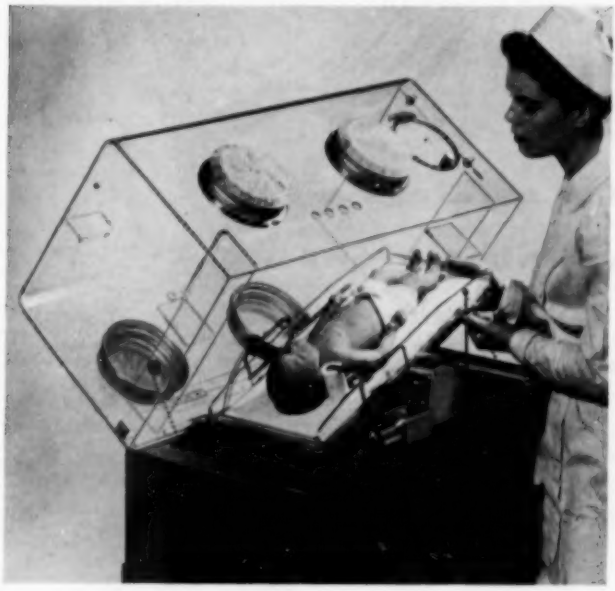

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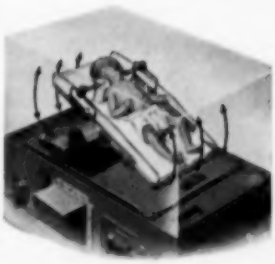

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A.M.A. JOURNAL OF
DISEASES OF CHILDREN

Acidosis and Coma in Juvenile Diabetics

THADDEUS S. DANOWSKI, M.D.; LAWRENCE GREENMAN, M.D.†; FRANKLIN A. WEIGAND, M.D., and FRANK M. MATEER, M.D., Pittsburgh

From published reports, including this one, it might be concluded that the formerly high death rate from acidosis and coma in juvenile diabetics [1-3] is reaching the vanishing point.[4-11] Such complacency is unjustified. Diabetes mellitus is the eighth cause of death in the 1- to 14-year age group,[12] and, though specific diagnoses are not available, it is highly probable that almost all of these deaths occur in acidosis and coma. These isolated fatalities, largely unreported in the pediatric literature, account for the bulk of more than 3000 deaths recorded during the past decade.[13] It is reasonable to presume that such deaths are largely preventable. We have reviewed our series of acidosis and coma for principles that might be applicable to these fatalities.

Materials and Methods

Criteria for the diagnosis of diabetic ketosis, acidosis, and coma vary.[4-8,10,14,15] To provide objective standards for comparison, we divide our cases in accord with the serum total CO_2 content at the time of admission. Values between 15.1 and 20.0 mEq. per liter are classified as ketosis. The term acidosis is reserved for patients with a serum total CO_2 content between 0 and 15.0 mEq. per liter. For purposes of comparison we further subdivide these into the 0-10 and 10.1-15.0 mEq. categories. Members of either of these two groups who are unconscious and unresponsive are said to be in coma.

In the interval between Jan. 1, 1948, (when the diabetic service was reorganized under full-time personnel) and Dec. 31, 1955, a total of 191 instances of acidosis or coma have been treated at the Children's Hospital of Pittsburgh. Of these, 130 were admitted with a serum total CO_2 content of 10 mEq. per liter or less; in the remaining 61 the serum total CO_2 content ranged between 10.1 and 15.0 mEq. per liter.

Results

A. *Frequency of Acidosis and Coma in Relation to the Total Diabetic Population*

Expressed in relation to the total diabetic load, one instance of acidosis or coma occurred per 58.4 months of diabetic care (191 episodes of acidosis or coma in the course of 11,168 patient-months in 422 juvenile diabetics). The majority of these were single admissions. However, 14 of the patients were admitted more than once. Among the recurrent group of acidosis-coma, two were admitted six times and four others were hospitalized five times each. Females predominated slightly in the total number of admissions (99 to 92), whereas in terms of individual patients nearly equal numbers of boys and girls were present, 69 and 71, respectively.

B. *Frequency of Acidosis and Coma in Relation to the Season and the Duration of Diabetes*

From Figure 1 it is evident that acidosis and coma occurred somewhat more fre-

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Established Investigator of the American Heart Association (Dr. Mateer).

From the Department of Research Medicine, University of Pittsburgh, the Renziehausen Memorial Ward and Clinic, and the Children's Hospital of Pittsburgh.

† Dr. Greenman died June 20, 1956.

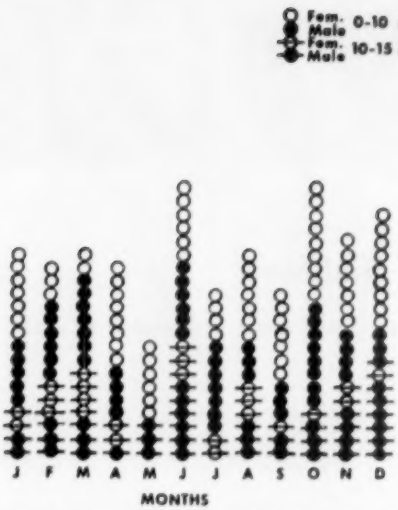

Fig. 1.—Frequency of admissions for diabetic acidosis and coma during the various months of the year.

quently during the winter months and that the lowest incidence was recorded in May. This is in keeping with the experience of Baker [8] and differs from that of Adams [16] and Spencer.[17] However, the total number of cases present in any month in each of these series, including our own, is probably too small to permit generalization.

In keeping with the findings of others,[4,11,18] acidosis or coma occurred more frequently during the first year of diabetes (Fig. 2). Almost one-third of the patients were previously unrecognized diabetics. The mean duration of diabetes in previously diagnosed cases who developed acidosis or coma was 4.48 and 4.65 years for the 0-10 and 10.1-15 mEq. (serum total CO_2 content on admission) groups, respectively. In contrast to the findings of Owens and Rockwern,[1] there was no evidence from the distribution of cases in our series (Fig. 2) that onset of diabetes during pubescence or adolescence is associated with a higher incidence of acidosis or coma.

C. *Antecedent and Presenting Symptoms and Clinical and Laboratory Findings*

In these 191 admissions a history of antecedent infection, usually of the respiratory type, was obtained in 61% (Table 1). In 31% the existence of diabetes was not recognized until acidosis or coma set in. In those in whom diabetes was known to be present a history of inadequate regulation,

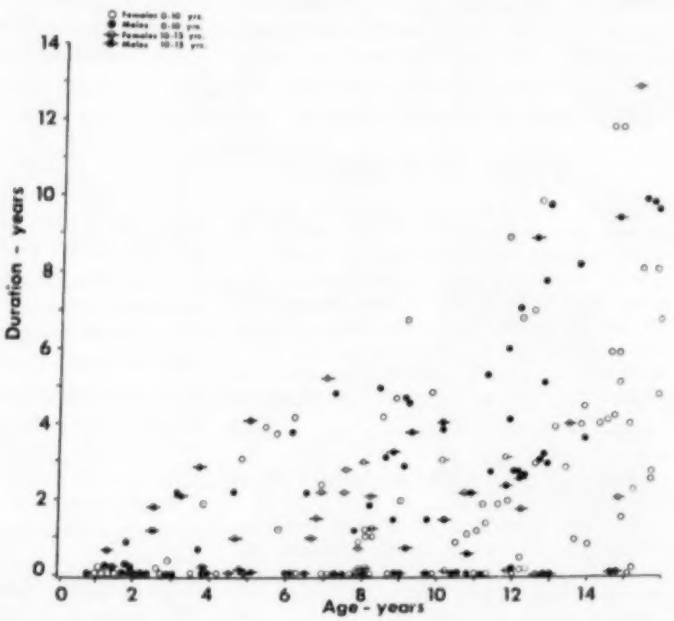

Fig. 2.—Incidence of acidosis and coma in relation to the duration of diabetes. Acidosis or coma occurred most frequently during the first year of diabetes and frequently proved to be the precipitating factor in making the diagnosis of diabetes.

TABLE 1.—*Antecedent and Presenting Symptoms and Signs in 191 Cases of Diabetic Acidosis and Coma*

CO_2 on Admission, mEq/L.	Per Cent of Total	Age, Years	Females, %	Prev. Undiagn, %	Poor Control, %	Insulin Omitted, %	Insulin Shock, %	Infections, %	Emot. Upset., %	Vomiting, %	Abd. Pain, %	Stupor, %	Frank Coma, %	Tachypnea,* %	Kussmaul Breathing, %
0-10	68	9.4	59	28	45	23	3	57	19	83	38	50	10	99	73
10.1-15	32	8.6	38	36	33	12	12	72	21	70	44	15	3	35	4
0-10 and 10.1-15	100	9.1	53	31	42	20	6	61	20	79	39	37	8	71	52

* Respiratory rates in excess of 24 per minute were taken to be tachypnea; during first hour of admission these ranged from 26 to 65 in the 0-10 and 10 to 68 in the 10.1-15 groups with mean values of 39 and 25, respectively.

TABLE 2.—*Glycosuria, Ketonuria, Albuminuria, Casts, and Leucocytosis in Diabetic Acidosis or Coma**

CO_2 on Admission, mEq/L.	4+ Glycosuria on Admission, % of Pts.	Ketone Bodies on Admission, Mean on 0-3+ scale†		Albuminuria on or After Adm.					Hyal. or Gran. Casts On or After Adm. (% of Pts.)	RBC in Urine On or After Adm. (% of Pts.)	Day of Admission		
		Acetone	Diacetic	0 (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)			WBC/Cu. Mm. Mean (No.) Max.-Min.	PMN/Cu. Mm.‡ Mean (No.) Max.-Min.	Lympho/Cu. Mm. Mean (No.) Max.-Min.
0-10	79	2.1	1.8	15	64	15	6	0	22	11	18,052 (49) 58,200-1,500	68 (49) 88-29	26 (49) 65-4
10.1-15	81	1.8	1.5	44	47	7	0	2	14	2	9,942 (12) 13,350-7,100	70 (12) 85-55	24 (12) 43-7

* Data on glycosuria and ketonuria available on all patients; complete urine analyses and blood cell counts could not always be obtained on day of admission.

† Mean value on scale of 0 to 3+; in the 0-10 group 8 patients had no acetone and 20 had no diacetic acid in urine on admission. In the 10.1-15 group the number of such negative tests were 7 and 10, respectively.

‡ Exclusive of an average of 4.2% and 3.6% metamyelocytes in the 0-10 and 10.1-15 groups, respectively.

as reflected in ketonuria and excessive glycosuria, was obtained in 42%. Insulin was omitted by 20% of the patients, an insulin shock preceded the acidosis in 6%, and a history of an emotional upset was recorded in one out of five patients.

Tachypnea (respiratory rate in excess of 24 per minute) was the commonest sign in the 0-10 mEq. per liter group with vomiting, Kussmaul breathing, stupor, abdominal pain, and coma next in the order of frequency. In the 10.1-15 mEq. per liter group these clinical manifestations were present in the following order of frequency: vomiting, abdominal pain, tachypnea, stupor, Kussmaul breathing, and coma (Table 1). Hence, though Kussmaul breathing is a much more frequent sign in the patients with the lower serum total CO_2 content, it is by no means an invariable finding and may appear occasionally in patients with 10.1-15 mEq. of CO_2 in serum. Tachypnea, on the other hand is almost always recorded when serum total CO_2 content is reduced below 10 mEq. per liter.

From Table 2 it is evident that 4+ glycosuria is not the invariable rule in either category and that as a matter of fact occasional aglycosuria or aketonuria may be encountered in patients with frank acidosis or coma. This reflects decreases in the clearance of these blood constituents as a consequence of decreased filtration or acute tubular damage and of course is not a new observation.[19] In this regard it is of interest to point out as others have done that transient albuminuria, up to 4+ in intensity on the basis of the ordinary heat and acetic acid test, accompanied by granular and hyaline casts and by erythrocytes may be present (Table 2). Finally, leukocytosis in excess of 50,000 per cubic millimeter, a polymorphonuclear increase, and lymphocytopenia may be found on the day of admission without infection or acute abdominal disease. This is in part attributable to the associated discharge of the adrenal cortex.[19]

D. *Therapy*

Immediately upon admission blood was withdrawn for analysis, 25 to 100 units of crystalline insulin was given, and an infusion of saline was started. Some of the more recent patients also received an intravenous infusion of dextran (6% to 10% of dextran in saline or in water).

At hourly intervals thereafter the original insulin dosages or smaller amounts were repeated. Saline infusions were continued; alkali solutions were not used routinely. At the end of three to five hours of therapy another sample of blood was obtained and buffered potassium phosphate in 5% glucose (dextrose) was started. A quantitative summary of therapy in the various age groups is shown in Table 3. These values fall within the ceiling values for water-electrolyte administration as suggested by Talbot et al.[23]

E. *Blood and Serum Solutes*

1. On Admission: The range of hyperglycemia, the variable and frequent increases in whole blood nonprotein nitrogen, the extent of serum total CO_2 decrease, the tendency to hyponatremia and hypochloremia, and the variable changes in serum potassium and inorganic phosphorus in the 0-10 mEq. per liter groups at zero time are shown in Figures 3 through 9. The mean values for these constituents and the serum protein, albumin, globulin, cholesterol, and calcium values in the 0-10 and 10.1-15 mEq. per liter groups are given together with normals in Table 4.[21]

On admission equivalent increases in blood sugar were present in both groups. NPN and cholesterol levels were somewhat more elevated in the 0-10 mEq. group. Hyponatremia and relative hypochloremia were present in both. Mean potassium values were only slightly above those seen in healthy children. There was no discernible change in the average albumin and glubulin concentrations, whereas the serum calcium and phosphorus values were higher than normal in both of the diabetic acidosis-coma groups. The analytic procedures em-

TABLE 3.—*Summary of Therapy in Diabetic Acidosis and Coma in Juvenile Diabetics Admitted with Serum Total CO_2 Content of 0-10, and 10.1-15 Milliequivalents per Liter*

	Age Group, Yr.	Average Age, Yr.	No. of Cases	Hours of Rx	Average Therapy
Insulin					
	0-4	2.2	22	22.5	76.5 units
0 to 10	4-8	6.4	14	20.4	78.8 units
mEq/L. group	8-12	9.9	34	20.2	146.4 units
	12-16	13.8	49	18.6	156.6 units
	0-4	2.6	6	8.2	41.7 units
10.1 to 15	4-8	6.0	8	26.4	71.5 units
mEq/L. group	8-12	9.8	12	15.1	66.8 units
	12-16	13.0	5	13.7	43.4 units
Na and Cl					
	0-4	2.1	20	22.2	167 mEq.
0 to 10	4-8	6.2	13	21.2	243 mEq.
mEq/L. group	8-12	10.1	34	19.4	228 mEq.
	12-16	13.9	44	16.3	297 mEq.
	0-4	2.6	5	8.1	117 mEq.
10.1 to 15	4-8	6.3	10	17.0	162 mEq.
mEq/L. group	8-12	10.1	12	15.8	245 mEq.
	12-16	13.0	5	13.6	162 mEq.
Water					
	0-4	2.1	21	21.6	2.1 liters
0 to 10	4-8	6.2	14	20.9	2.8 liters
mEq/L. group	8-12	10.0	35	19.0	2.9 liters
	12-16	13.9	44	16.3	3.2 liters
	0-4	2.6	5	8.1	1.4 liters
10.1 to 15	4-8	6.3	10	17.0	2.5 liters
mEq/L. group	8-12	10.1	12	15.8	2.7 liters
	12-16	13.0	5	13.6	2.2 liters
Glucose					
	0-4	2.1	21	21.6	99.7 gm.
0 to 10	4-8	6.2	14	20.9	162.9 gm.
mEq/L. group	8-12	10.0	35	19.0	154.4 gm.
	12-16	13.9	43	16.3	147.9 gm.
	0-4	3.0	4	9.1	56.2 gm.
10.1 to 15	4-8	6.7	8	19.1	104.4 gm.
mEq/L. group	8-12	10.1	10	18.1	136.8 gm.
	12-16	13.0	5	13.6	88.2 gm.
Potassium					
	0-4	2.3	9	21.8	53 mEq.
0 to 10	4-8	7.4	5	30.1	64 mEq.
mEq/L. group	8-12	10.1	18	22.2	73 mEq.
	12-16	14.2	18	19.9	59 mEq.
	0-4	2.5	1	10.5	60 mEq.
10.1 to 15	4-8	8.0	1	10.0	15 mEq.
mEq/L. group	8-12	9.7	4	24.2	82 mEq.
	12-16	11.9	1	5.5	40 mEq.
Phosphate					
	0-4	2.3	7	18.6	51.1 mEq.
0 to 10	4-8	7.4	4	28.6	60.0 mEq.
mEq/L. group	8-12	10.0	16	22.3	71.9 mEq.
	12-16	14.1	17	19.3	60.6 mEq.
	0-4	2.4	1	10.5	60.0 mEq.
10.1 to 15	4-8	8.0	1	10.0	15.0 mEq.
mEq/L. group	8-12	9.7	4	24.2	82.5 mEq.

ployed have been described in previous publications from this laboratory.[22,24]

2. During Therapy: Administration of insulin, saline, and of dextran in some patients, and subsequently of glucose, potassium, and phosphate, as described in section D, reduced the whole blood NPN down to or below the normal range, decreased the blood sugar levels, permitted the serum total CO_2 content to rise (Figs. 3 through 5), cancelled the hyponatremia and hypochloremia and at times produced hypernatremia and hyperchloremia (Figs. 6, 7), and resulted in many patients in an early hypokalemia and hypophosphatemia with subsequent rises toward or to normal (Figs. 8, 9).

F. *Disappearance of Symptoms and Signs*

Kussmaul overbreathing when present disappeared in an average of 5.4 to 8 hours in the 4- to 16-year-old groups. Data on the 0- to 4-year-old group are lacking. Ketonuria cleared in 11.2 to 16.2 hours in

TABLE 4.—*Mean Values of Blood and Serum Constituents on Admission of the 0-10 and 10.1-15 Milliequivalents CO_2 Groups Compared with Fasting Levels in Healthy Nondiabetic Children*

		0-10 mEq/L. Mean±S.D. (Max.-Min.)	(No.)	10.1-15 mEq/L. Mean±S.D. (Max.-Min.)	(No.)	Healthy Nondiabetics* Mean±S.D.
Bl. sugar	(mg. per 100 cc.)	429±178.0 (1180-42)	(131)	420±358.6 (2500-76)	(55)	----
NPN	(mg. per 100 cc.)	44±14.3 (104-19)	(111)	41±15.6 (100-19)	(49)	----
Serum CO_2	(mEq/L.)	6.2±2.0 (10.0-2.0)	(131)	12.8±1.2 (15.0-10.1)	(60)	23.1±1.3
Cl	(mEq/L.)	99.4±7.1 (121.8-84.4)	(123)	93.7±20.3 (114.2-79.1)	(52)	103.3±3.0
Na	(mEq/L.)	136±6.9 (151-121)	(81)	136±6.0 (144-117)	(35)	144±3.0
K	(mEq/L.)	4.8±0.94 (6.6-1.6)	(81)	4.6±0.70 (6.7-2.2)	(35)	4.3±0.4
Alb.	(gm. per 100 cc.)	4.24±0.83 (5.4-1.3)	(44)	4.22±0.86 (5.6-1.9)	(26)	4.26±0.58
Glob.	(gm. per 100 cc.)	2.95±0.82 (4.6-0.79)	(44)	3.12±0.60 (4.7-2.5)	(25)	3.0±0.55
Ca	(mg. per 100 cc.)	10.7±1.04 (13.4-8.4)	(34)	10.5±0.83 (11.8-9.2)	(24)	9.8±0.4
Phos.	(mg. per 100 cc.)	5.51±1.87 (11.2-1.01)	(63)	4.90±1.41 (9.1-1.8)	(29)	4.76±0.41
Chol.	(mg. per 100 cc.)	341±167.6 (1066-163)	(44)	306±116.7 (738-145)	(26)	229±42

* The entire population of the Protestant Home for Children totaling 70 members. Samples of venous blood were obtained prior to breakfast while at bed rest one or more times.

the 0-4, 4-8, 8-12, and 12-16-year age groups admitted with serum total CO_2 content of 10 mEq. per liter or lower. This took somewhat longer in the 10.1-15 mEq. group, 11.9 to 25.9 hours, presumably because therapy was less intensive. Oral intake was resumed on the average between the 12th and 17th hours in the various age groups admitted with a CO_2 content of less than 10 mEq. per liter, and between the 5th and 9th hours in the others.

G. *Mortality*

There were five deaths in this group of 191 patients, all in previously undiagnosed

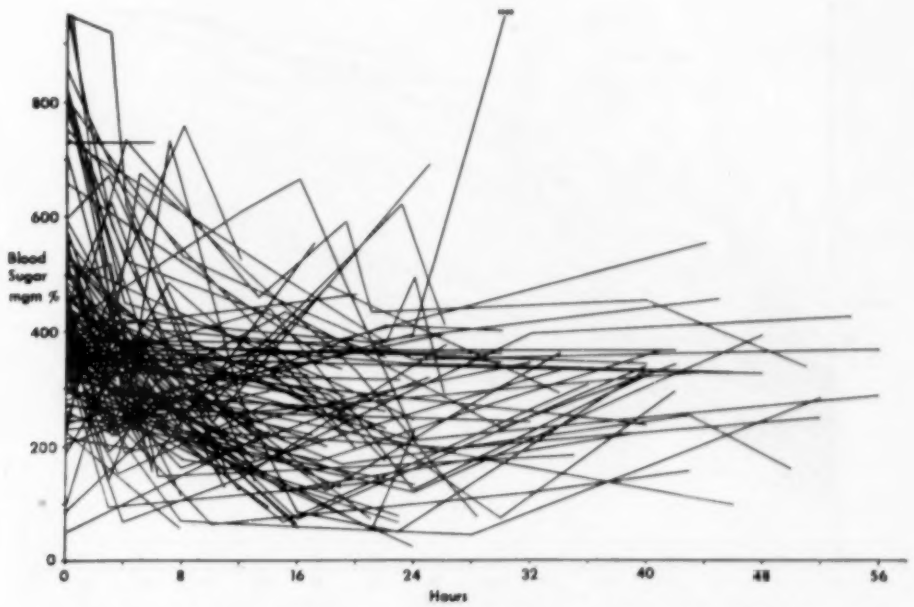

Fig. 3.—Admission and subsequent venous blood sugar values in the 0-10 mEq. of CO_2 per liter group of acidosis-coma patients.

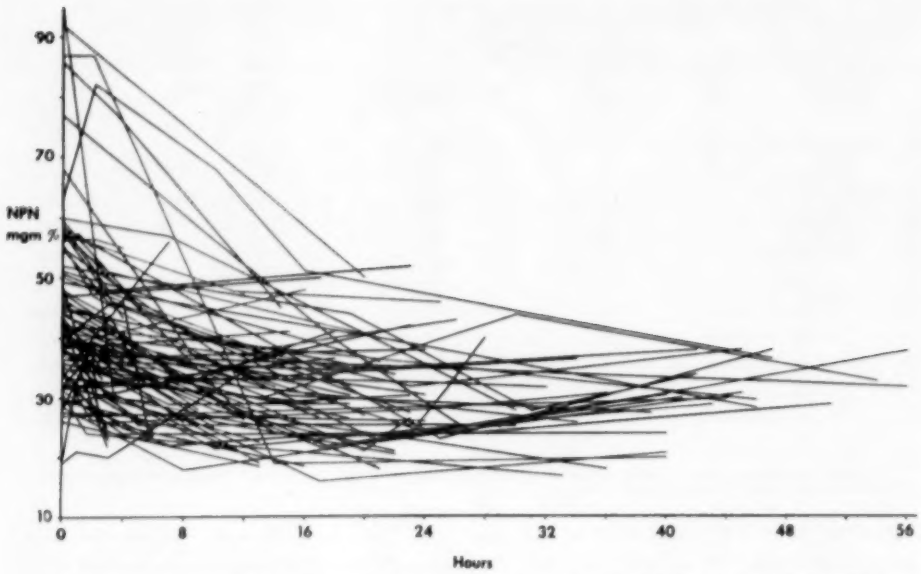

Fig. 4.—Elevations and subsequent decreases in whole blood NPN levels in 0-10 mEq. of CO_2 per liter group of acidosis and coma.

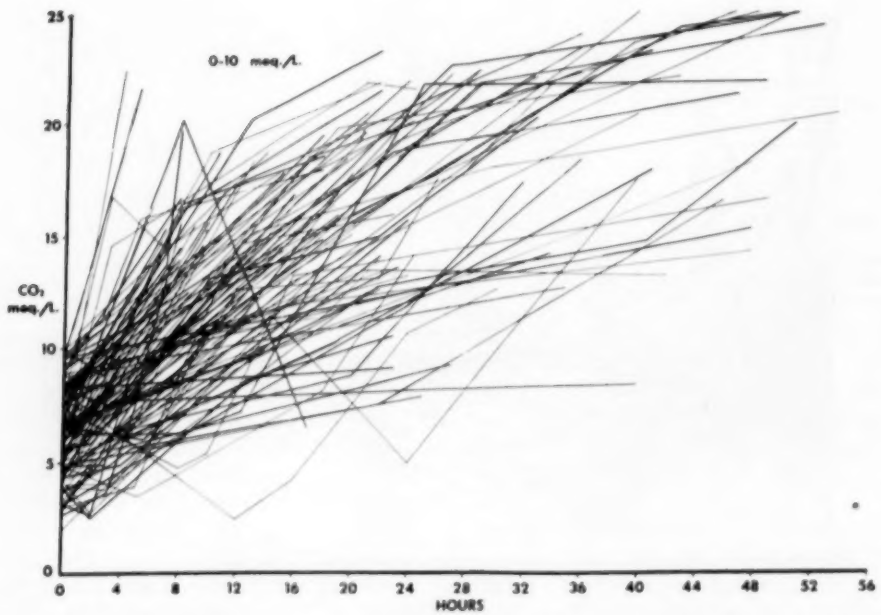

Fig. 5.—Changes in Admission levels of serum total CO_2 content during therapy in 0-10 mEq. per liter group.

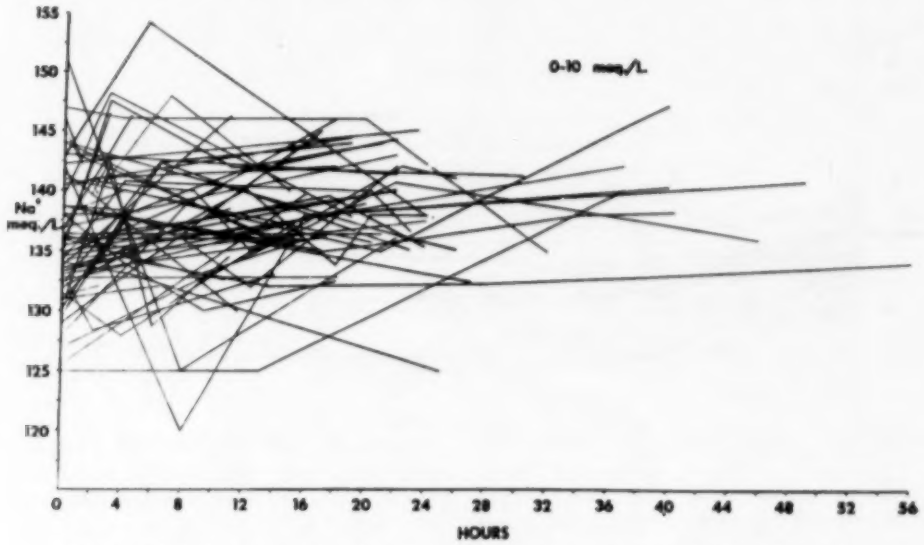

Fig. 6.—Variable concentrations in serum sodium on admission of 0-10 mEq. CO_2 per liter group of acidosis-coma patients. The rises in serum sodium are attributable to retention of administered sodium in excess of water and vice versa in those showing a decrease.

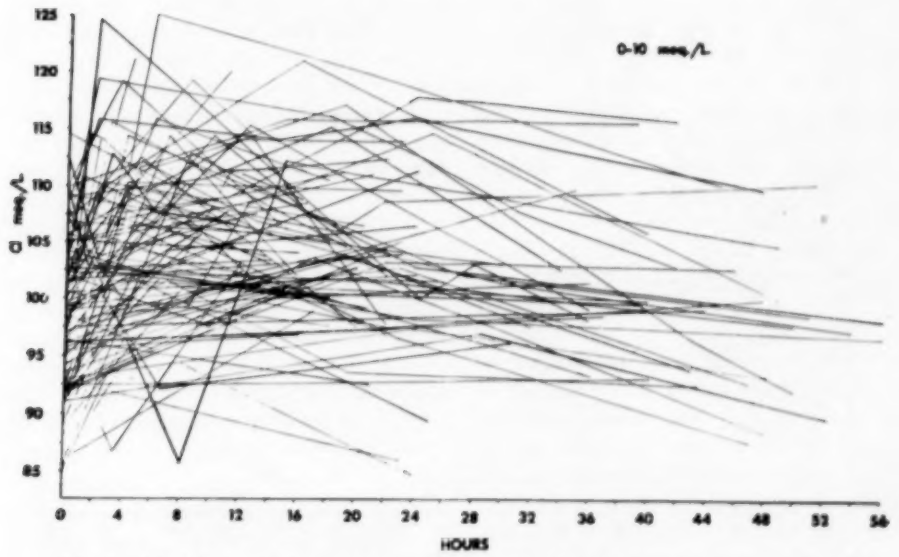

Fig. 7.—Admission and subsequent serum Cl levels in acidosis and coma in patients admitted with serum total CO_2 content of 10 mEq. per liter or less. Same comments as those made in the case of sodium apply here.

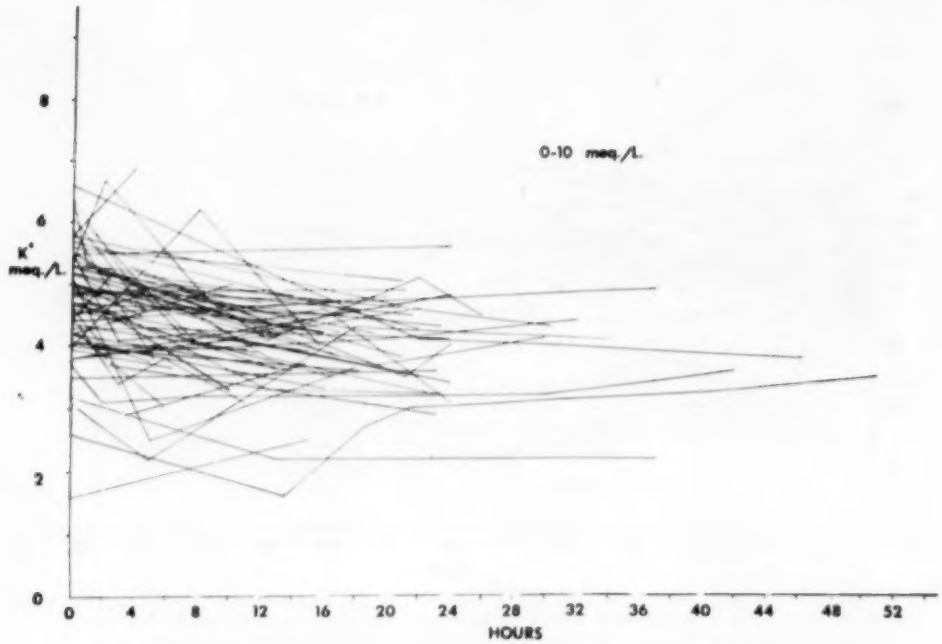

Figure 8.—Hyperkaliemia, hypokaliemia, and normal serum potassium levels in acidosis-coma. On admission this group of children with initial serum total CO_2 content of 10 mEq. per liter or less had variable levels of potassium. This contrasts with the greater tendency toward hyperkaliemia in adult patients. With treatment high and low values tended to return to normal despite the fact that all patients received potassium.

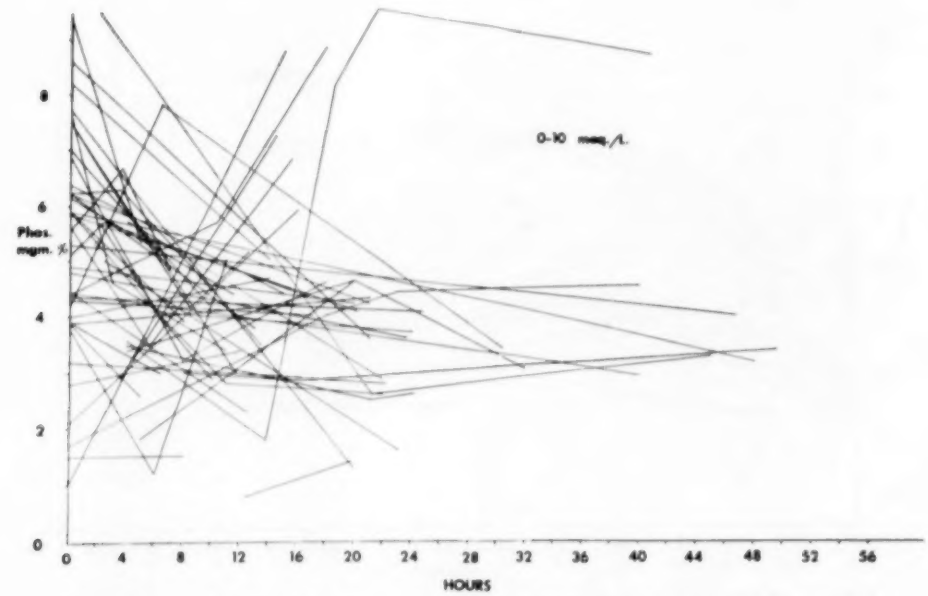

Fig. 9.—Serum inorganic phosphorus may be high, normal, or low on admission in acidosis or coma. Subsequent changes attributable to net external and internal balances of phosphorus and of water.

TABLE 5.—*Deaths in Juvenile Diabetic Acidosis and Coma in Children's Hospital of Pittsburgh Series (1948-1955), All in Previously Undiagnosed Patients*

Pt.	Sex	Age	Presenting Symptoms	Duration of Presenting Symptoms	Interval in CHP Before Death
1	M	13 mo.	Transferred to CHP with thirst, polyuria, 6 lb. wt. loss, 3 days overbreathing after Rx of otitis and development of penicillin rash in another hospital	1 mo.	3 hr.
2	F	10 yr. 4 mo.	Admitted with overbreathing, sore throat, and unconsciousness of one day's duration after several weeks of oral therapy by faith healer for weight loss	3 mo.	2 hr. 45 min.
3	M	12 yr.	Pt. admitted with weight loss (8 lb.), weakness (4 days), headache (24 hr.), polyuria, and polydypsia; blood sugar: 2500 mg. per 100 cc.	1 wk.	4 hr.
4	M	11 yr. 2 mo.	Pt. with known muscular dystrophy admitted with sore throat, vomiting, coma; died in congestive heart failure and at autopsy had muscular dystrophy of heart	4 days	10 hr. 10 min.
5	F	4 yr. 1 mo.	Transferred from another hospital with history of polyuria, polydypsia, and coma of several hours duration	4 days	1 hr. 40 min.

diabetics. Pertinent clinical data are summarized in Table 5. It is to be noted that prolonged delays in diagnosis, often in other hospitals, were present in each case, that each patient entered moribund, and that death ensued in ¼ to 10 hours. The overall mortality in our series of 191 cases was 2.6%

Comment

Our records indicate that in an unselected series of children admitted in diabetic acidosis or coma all previously known diabetics recover and that even in the newly discovered diabetics deaths occur only in those in whom diagnosis and therapy have been unduly delayed. Though equally effective variants of diabetic acidosis and coma therapy of the type employed in other clinics could have been used, it is probable that the five deaths could not have been prevented by such variables. As a matter of fact in those who died these variants were used, i. e., alkali and plasma volume expanders were given. Hence it is evident that if acidosis and coma deaths in juvenile diabetics are to be prevented the child should be a previously known diabetic so that therapy can be instituted promptly.

A. *Insulin*

Agreement is general that such patients should receive rapid-acting insulin in amounts sufficient to restore the metabolism of carbohydrate, fat, and protein toward or to normal. Our experience as recorded in Table 3 provides a guide to the total amounts used in the various age groups during the first day of therapy. These values serve as approximate indices only, and the individual prescription may have to be lowered or raised depending on the responses of the blood or serum sugar, the serum total CO_2 content, the serum acetone, and the urinary glucose and ketone bodies. As a rule of thumb, however, it would appear that a child falling into the 0- to 8-year-old group should receive 25 to 50 units as the initial injection of rapid-acting insulin. The older children ought to be given 50 to 100 units. This amount can be injected even before transporting the patient to the hospital. Obviously if this is considerably less than the patient's usual daily dosage correspondingly larger amounts should be given. If the insulin is first administered after admission, one-half of the dosage can be injected intravenously, thereby accelerating the onset of its action. The size of the second dosage of insulin given at the end of the first hour of therapy is determined by the results of the analysis of the admission blood and serum. It may be as large as the first injection, larger, or smaller. During the third and fourth hour smaller amounts of insulin are usually given. Repeat analyses of blood and serum just before the end of the fourth hour, and at approximately the same intervals thereafter, provide

guides for maintaining, accelerating, or tapering further insulin therapy.

B. *Water and Sodium Salts*

It is also universally agreed that water and sodium salts should be given immediately upon admission to cancel the deficits of these body constituents. Repletion studies in this and other laboratories indicate that the deficit of water in terms of volume is equal to approximately 10% of the body weight, and that the losses of sodium average 5 to 13 mEq. per kilogram of body weight.[22,23,25,26] The deficits of chloride are somewhat less than those of sodium. It is not our custom to use alkalinizing salts routinely, i. e., sodium bicarbonate or one-sixth molar sodium lactate, because this deprives the therapist of the rise in serum total CO_2 content as an index of response. We do, however, administer these salts to desperately ill patients with marked reduction in pH, i. e., to 7.2 or lower. It has been our experience and that of others with low mortality records [4-6] that this is not an essential therapy in all patients and that alkalosis may thereby be precipitated at a time when the serum total CO_2 content is still low.[27,28]

On the other hand, the routine use of 0.9% sodium chloride will provide too much chloride and may impose a hyperchloremic acidosis on the metabolic acidosis. This is not a problem if the total volume of 0.9% sodium chloride is limited and the patient receives glucose in water. Alternatively, hypotonic solutions of sodium and chloride [20,29,30] may be given, though these can produce hypotonicity, water intoxication, and convulsions; Ringer's lactate solution which provides less chloride than sodium (though this is of course alkalinizing) may also be used. Irrespective of the form in which the water, sodium, and chloride solutions are administered, it is very helpful to utilize the ceiling values of Talbot et al. referred to earlier [20] as a guide to the rate and total volumes of infusion. Thus, the child with intact homeostatic regulation can readily dispose of some 3 liters of water, 225 mEq. of sodium, and a similar amounts of potassium and of chloride per square meter of body surface area in 24 hours. Tables for estimating surface area are readily available.[31] It should be kept in mind that larger volumes can be safely given when deficits are present and must be given when renal losses continue as they do during therapy of diabetic coma.

C. *Colloid*

Diabetic acidosis or coma patients who enter the hospital in circulatory collapse benefit from the administration of colloid (blood, plasma, and other plasma-volume expanders) in addition to replacement of the water and extracellular electrolyte stores,[32] indicating an additive effect of colloid and saline in the treatment of salt depletion shock. Experiments in animals provide a rational basis for such combined therapy.[33] On the other hand, the onset of oliguria or anuria is a signal for more precise regulation of the input, since the kidneys cannot be expected to make the necessary adjustments for excesses of fluid therapy.

D. *Use of Glucose or Fructose*

In contrast to earlier controversial views [34,35] it is now generally granted that glucose should be administered when the blood sugar is falling in the course of acidosis and coma therapy. It had been suggested that ample stores of glucose are already present in acidosis and coma patients.[36] This is not true, since glycogen stores are depleted,[37,38] and the high levels of blood and extracellular glucose provide only a limited source of carbohydrate. The latter amounts to 35 gm. in a 35-kg. child with a glucose concentration of 500 mg. per 100 cc. in the blood and the extracellular fluid. It is not our custom to give glucose routinely on admission, but we don't hesitate to administer it if the blood sugar is low at the start of therapy, i. e., less than 300 mg. per 100 cc., as it is in some children (Fig. 4). In addition to hastening the action of insulin early in therapy and preventing later hypoglycemia, glucose solutions provide water for replacement of body stores. There is, however, no place for aqueous

solutions of glucose administered subcutaneously in the therapy of acidosis and coma, since extracellular sodium and chloride are thereby segregated in the subcutaneous pool and salt depletion is aggravated.[39,40] Similarly, such aqueous electrolyte-free solutions of glucose should not be given intravenously at the start of therapy when the blood sugar is low, since they will precipitate the symptoms of water intoxication. Hence for early use we prefer to give the glucose in 0.9% saline, or in Ringer's lactate, or in concentrated form in water. Once the sodium and chloride stores have been replaced, the dilute aqueous glucose solution can be given safely by vein. The concentration of glucose can vary from 5% to 50%, and the dosage can be calculated from the increase desired, using 15% or 20% of the body weight as an estimate of the extracellular fluid volume in which glucose distributes itself.

Is fructose therapy of advantage in diabetic acidosis and coma? This sugar can enter the glycolytic cycle without the intervention of insulin and is a better glycogen former than glucose.[19] These properties, added to the fact that the tubular reabsorption of glucose and fructose is nonadditive,[41] suggest that distinct advantages might accrue from the routine use of fructose in acidosis and coma.[42-47] However, some studies indicate that adrenocortical discharge, a common feature of acidosis,[48,49] mitigates the theoretical advantages of fructose.[50] Also, fructose does not appear to enter extrahepatic cells readily.[51] Finally, fructose which enters the glycolytic cycle is largely converted to glucose. At present, therefore, the advantages of fructose appear to be greater theoretically than practically.

E. *Administration of Potassium and of Phosphate*

In the studies cited earlier [22,23,25,26] it has been estimated that the potassium deficit in diabetic acidosis or coma in children is 5 to 6 mEq. per kilogram of body weight. It is obvious, therefore, that the goal of therapy should be provision of an input or intake of this electrolyte sufficiently in excess of the losses in urine to permit repletion. It is well to know the serum levels of potassium, and to obtain evidence of adequate urinary output and renal function before starting potassium. In our clinic, therefore, potassium is not given ordinarily until the end of the fourth hour, when it is administered as buffered phosphate (KH_2PO_4:K_2HPO_4), 40 mEq. per liter in 5% glucose, for a total initial dosage of 20 to 60 mEq. The average total amounts of potassium and of phosphate administered to the various age groups ranged from 40 to 80 mEq. during the first day of therapy or fraction thereof (Table 2). Use of the phosphate salt permits repletion of this constituent [52-55] and avoids the administration of further chloride.

Summary and Conclusions

In a nine-year period 191 instances of diabetic acidosis or coma occurred in 140 children in the course of treating a total of 422 juvenile diabetics during a total of 11,168 patient-months. This represents one episode per 58.4 patient-months.

Antecedent events in order of frequency consisted of infections, inadequate control of known diabetes, unrecognized symptoms and signs of diabetes culminating in acidosis or coma, omission of insulin, and major emotional upsets.

In the group as a whole vomiting and tachypnea were the commonest clinical manifestations; Kussmaul breathing, abdominal pain, stupor, and coma were next in order of occurrence. The frequency of some of these findings varied with the degree of depression of the serum total CO_2 content.

Glycosuria and ketonuria need not be maximal and may even be absent. Albuminuria, the presence of hyaline or granular casts and red blood cells in the urine, and leukocytosis may be features of essentially uncomplicated acidosis or coma.

Patients with acidosis or coma in this series usually responded promptly to ther-

apy with insulin, saline, and glucose; colloid in the form of dextran was given to patients in circulatory collapse and prophylactically to a minority of the others; alkalinizing solutions were used only when the pH was markedly lowered.

The mortality was less than 3%.

Since all the deaths occurred in previously undiagnosed diabetics, prompt recognition of the onset of diabetes and institution of a control program should lower the incidence and the mortality rate of acidosis and coma.

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Addendum

In the interval between the preparation of the data in this paper and Dec. 15, 1956, we have treated 47 additional cases of diabetic acidosis coma without fatality. Sixteen of these were admitted with serum CO_2 content of 0-10 mEq. per liter and the remainder fell into the 10.1-15.0 mEq. per liter group.

REFERENCES

1. Owens, L. B., and Rockwern, S. S.: Prognosis in Diabetic Coma: Basic Importance of Mental State, Am. J. M. Sc. 198:252, 1939.

2. Harwood, R.: Diabetic Acidosis: Results of Treatment in 67 Consecutive Cases, New England J. Med. 245:1, 1951.

3. Collen, M. F.: Mortality in Diabetic Coma, Arch. Int. Med. 70:347, 1942.

4. Joslin, E. P.; Root, H. F.; White, P.; Marble, A., and Hunt, H. M.: Diabetic Coma, M. Clin. North America 16:793, 1932.

5. Joslin, E. P.; Root, H. F.; White, P.; Marble, A., and Joslin, A. P.: Diabetic Coma, Arch. Int. Med 59:175, 1937.

6. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: Diabetic Coma, J. A. M. A. 119:1160, 1942.

7. Bowen, B. D., and Hekimian, I.: Diabetic Coma: A Report of 81 Instances, Ann. Int. Med. 3:1111, 1930.

8. Baker, T. W.: A Clinical Survey of 108 Consecutive Cases of Diabetic Coma, Arch. Int. Med. 58:373, 1936.

9. Hagtvet, J.: Diabetic Coma: A 9 Year Statistical Record, Acta med. scandinav. 114:168, 1943.

10. Dillon, E. S., and Dyer, W. W.: Factors Influencing the Prognosis in Diabetic Coma, Ann. Int. Med. 11:602, 1937.

11. Beardwood, J. T., Jr., and Rouse, G. P., Jr.: Diabetic Acidosis: A Study of 220 Consecutive Cases, J. A. M. A. 117:1701, 1941.

12. Monthly Vital Statistics Report, United States Department of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics 3:16, 1955.

13. Vital Statistics, Special Reports, National Summaries, Death and Death Rates for Selected Causes by Age, Race, and Sex, United States, Federal Security Agency, Public Health Service, National Office Vital Statistics 29:19, 23, 1948; 31:125, 139, 1949; 35:325, 339, 1950; 38:68, 74, 1954; 37:297, 317, 1953; 40:6, 12, 1954; 42:66, 1955.

14. Joslin, E. P.: Diabetic Coma, Pennsylvania M. J. 56:353, 1953.

15. Sprague, R. G.: Diabetic Acidosis and Coma, M. Clin. North America 31:445, 1947.

16. Adams, S. F.: The Seasonal Variation in the Onset of Acute Diabetes: Age and Sex Factors in 1000 Diabetic Patients, Arch. Int. Med. 37:861, 1926.

17. Spencer, H.: Diabetes Mellitus in Children: Studies of the Height and Weight of 45 Patients, Am. J. Dis. Child. 36:502, 1928.

18. Nelson, W. E.: Textbook of Pediatrics, Philadelphia, W. B. Saunders Company, 1954, pp. 1275-1286.

19. Danowski, T. S.: Diabetes Mellitus, with Emphasis on Children and Young Adults, Baltimore, Williams & Wilkins Company, 1957, Chaps. 18, 19, and 20.

20. Talbot, N. B.; Crawford, J. D., and Butler, A. M.: Medical Progress: Homeostatic Limits to Safe Parenteral Fluid Therapy, New England J. Med. 248:1100, 1953.

21. Elkinton, J. R., and Danowski, T. S.: The Body Fluids: Basic Physiology and Practical Therapeutics, Baltimore, Williams and Wilkins Company, 1955, Chap. 4.

22. Danowski, T. S.; Peters, J. H.; Rathbun, J. C.; Quashnock, J. M., and Greenman, L.: Studies in Diabetic Acidosis and Coma, with Particular Emphasis on Retention of Administered Potassium, J. Clin. Invest. 28:1, 1949.

23. Greenman, L.; Mateer, F. M.; Gow, R. C.; Peters, J. H., and Danowski, T. S.: Some Obser-

vations on Development of Hypokaliemia During Therapy of Diabetic Acidosis in Juvenile and Young Adult Subjects, J. Clin. Invest. 28:409, 1949.

24. Danowski, T. S.; Greenman, L.; Mateer, F. M.; Parsons, W. B.; Weigand, F. A.; Mermelstein, H., and Peters, J. H.: Carboxylic Cation Exchange Resin Effects in Dogs, J. Clin. Invest. 30:984, 1951.

25. Butler, A. M.; Talbot, N. B.; Burnett, C. H.; Stanbury, J. B., and MacLachlan, E. A.: Metabolic Studies in Diabetic Coma, Tr. A. Am. Physicians 60:102, 1947.

26. Darrow, D. C., and Pratt, E. L.: Retention of Water and Electrolyte During Recovery in a Patient with Diabetic Acidosis, J. Pediat. 41:688, 1952.

27. Singer, R. B., and Hastings, A.B.: Improved Clinical Method for Estimation of Disturbances of Acid-Base Balance of Human Blood, Medicine 27:223, 1948.

28. Bock, A. V.; Field, H., Jr., and Adair, G. S.: Acid-Base Equilibrium in Diabetic Coma, Being a Study of 5 Cases Treated with Insulin, J. Metabolic Res. 4:27, 1923.

29. Butler, A. M.: Medical Progress: Diabetic Coma, New England J. Med. 243:648, 1950.

30. Kerrigan, G. A.; Crawford, J. D.; Sceery, R. T.; Heeley, A.; Terry, M., and Talbot, N. B.: Concerning Importance of Homeostatic Systems in Recovery of Patients Requiring Parenteral Fluid Therapy, Society Transactions, A. M. A. Am. J. Dis. Child. 86:622, 1953.

31. Talbot, N. B.; Sobel, E. H.; McArthur, J. W., and Crawford, J. D.: Functional Endocrinology, from Birth Through Adolescence, Cambridge, Mass., Harvard University Press, 1952, pp. 597.

32. Danowski, T. S.; Winkler, A. W., and Peters, J. P.: Salt Depletion, Peripheral Vascular Collapse, and Treatment of Diabetic Acidosis, Yale J. Biol. Med. 18:405, 1946.

33. Winkler, A. W.; Danowski, T. S., and Elkinton, J. R.: Role of Colloid and of Saline in Treatment of Shock, J. Clin. Invest. 25:220, 1946.

34. Root, H. F.: Anuria Following Diabetic Coma Relieved by Hypertonic Salt Solution, J. A. M. A. 103:482, 1934.

35. Root, H. F.: Use of Glucose in Treatment of Diabetic Coma, J. Clin. Endocrinol. 5:353, 1945.

36. Soskin, S., and Levine, R.: Physiological and Clinical Aspects of Ketosis, Am. J. Digest. Dis. 11:305, 1944.

37. Bondy, P. K.; Sheldon, W. H., and Evans, L. D.: Changes in Liver Glycogen Studied by Needle Aspiration Technic in Patients with Diabetic Ketosis, with Method for Estimation of Glycogen from Histologic Preparations, J. Clin. Invest. 28: 1216, 1949.

38. Bondy, P. K., and Sheldon, W. H.: Histochemical Demonstration of Liver Glycogen in Human Diabetic Acidosis by Liver Biopsy, Proc. Soc. Exper. Biol. & Med. 65:68, 1947.

39. Danowski, T. S.; Winkler, A. W., and Elkinton, J. R.: The Treatment of Shock Due to Salt Depletion: Comparison of the Hemodynamic Effects of Isotonic Saline, of Hypertonic Saline, and of Isotonic Glucose Solutions, J. Clin. Invest. 25:130, 1946.

40. Danowski, T. S.; Winkler, A. W., and Elkinton, J. R.: Biochemical and Hemodynamic Changes Following Subcutaneous Injection of Glucose Solution, J. Clin. Invest. 26:887, 1947.

41. Moncrief, J. A.; Coldwater, K. B., and Elman, R.: Postoperative Loss of Sugar in Urine Following Intravenous Infusion of Fructose (Levulose), A. M. A. Arch. Surg. 67:57, 1953.

42. Miller, M.; Drucker, W. R.; Owens, J. E.; Craig, J. W., and Woodward, H., Jr.: Comparison of Metabolic Effects of Fructose and Glucose Administered Intravenously to Normal and Diabetic Subjects, J. Lab. & Clin. Med. 38:931, 1951.

43. Miller, M.; Murphy, J. R.; Craig, J. W., and Woodward, H., Jr.: Studies in Experimental Diabetic Acidosis: Comparison of Effect of Fructose and Glucose in Initial Hours of Treatment, J. Clin. Endocrinol. 13:866, 1953.

44. Darragh, J. H.; Womersley, R. A., and Meroney, W. H.: Fructose in Treatment of Diabetic Ketosis, J. Clin. Invest. 32:1214, 1953.

45. Klinger, R., and Dalle Coste, P.: Use of Fructose in Diet and Treatment of Patients with Diabetes Mellitus, Minerva med. 46:1389, 1955.

46. Dolger, H.; Kupfer, S.; Bookman, J. J., and Carr, J.: Intravenous Fructose in Diabetes Mellitus: Advantages Over Glucose in the Treatment of Diabetic Emergencies, J. Clin. Invest. 32:562, 1953.

47. Seltzer, H. S., and Conn, J. W.: Fructose Metabolism in Diabetes: Clinical Applications, J. Michigan M. Soc. 52:1095, 1953.

48. McArthur, J. W.; Smart, G. A.; MacLachlan, E. A.; Terry, M. L.; Harting, D.; Gautier, E.; Godley, A.; Swallow, K. A.; Simeone, F. A.; Zygmuntowicz, A.; Christo, E.; Crepeaux, J.; Point, W. W., and Benson, J. A., Jr.: Studies Concerning Role of Adrenal Cortex in Pathologic Physiology of Diabetic Acidosis: Temporal Rela-

tions Between Metabolic Events of Experimental Diabetic Acidosis and Level of Adrenal Cortical Function, J. Clin. Invest. 33:420, 1954.

49. Greenman, L.; Danowski, T. S.; Rosenbloom, M., and Holt, J.: 17-Ketosteroid Excretion During Therapy of Diabetic Acidosis, Fed. Proc. 10:55, 1951.

50. Tagnon, R. F., and Devreux, S.: Effect of Intravenous Injection of Fructose, With and Without ACTH Administration, on the Level of Blood Glucose, J. Clin. Endocrinol. 15:1475, 1955.

51. Wick, A. N.; Sherrill, J. W., and Drury, D. R.: The Metabolism of Fructose by the Extrahepatic Tissues, Diabetes 2:465, 1953.

52. Guest, G. M.: Organic Phosphates of Blood and Mineral Metabolism in Diabetic Acidosis: President's Address, Am. J. Dis. Child. 64:401, 1942.

53. Franks, M.; Berris, R. F., and Kaplan, N. O.: Phosphorus Metabolism in Diabetic Coma, J. Clin. Invest. 25:923, 1946.

54. Danowski, T. S.; Hald, P. M., and Peters, J. P.: Sodium, Potassium and Phosphates in Cells and Serum of Blood in Diabetic Acidosis, Am. J. Physiol. 149:667, 1947.

55. Franks, M.; Berris, R. F.; Kaplan, N. O., and Myers, G. B.: Metabolic Studies in Diabetic Acidosis: II. Effect of Administration of Sodium Phosphate, Arch. Int. Med. 81:42, 1948.

The Pathological Changes in the Liver in Cystic Fibrosis of the Pancreas

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Once cystic fibrosis of the pancreas had been recognized as a clinical and pathological entity, histological alteration of the liver was found to be a common feature of the total process [1-3] with qualitative and quantitative differences. The basic liver lesions described have included liver-cell atrophy, fatty metamorphosis, periportal fibrosis, and proliferation of the bile ducts, often distended by obstructing bile plugs.[1-7] In certain more advanced cases, a focal biliary cirrhosis was found, and this has been considered by most to be due to the focal obstructive lesions resulting from the altered and inspissated bile-containing mucus plugs in the dilated terminal radicles.[1-3,5,7-13] *

This report is a review of the clinical records and postmortem material of 198 autopsied cases of cystic fibrosis of the pancreas. An attempt is made to define the liver changes, to indicate the pathogenesis, and to relate their changes noted to the total clinical picture in this diffuse metabolic disorder.

Methods and Materials

A survey of the listed postmortem diagnoses for the years 1918-1956, including cystic fibrosis of the pancreas, meconium ileus, chronic pulmonary suppuration, bronchiectasis, or pulmonary abscesses, was made and the sections of the pancreas examined from all of these cases. Those cases which contained the classic histological alterations in the pancreas of (1) fibrosis, (2) inspissation of secretion in the acini and ducts, (3) atrophy and dilatation of these structures, (4) replacement of the glandular substance by adult fat cells, and (5) the presence of only moderate degrees of acute pancreatitis were included. Those cases in which the inflammatory reaction was not accompanied by cystic and fibrotic changes were excluded.

In all cases the clinical histories were reviewed to obtain corroborative data to establish the diagnosis and to evaluate the histological changes in light of the patient's age, duration of disease, evidence of liver dysfunction, method of treatment, and clinical nutritional status. The clinical history of meconium ileus was considered to be strongly suggestive but not diagnostic of the disease. Although it is agreed that practically all infants with meconium ileus will develop the other clinical features of cystic fibrosis if they survive for a sufficient length of time, the two cases of meconium ileus not having the critical pathological features were not included in the final figures.[14] The history of chronic diarrhea, especially with bulky, foul stools, failure to gain weight, recurrent pulmonary infections with emphysema and abscess formation, was considered as positive evidence in the diagnosis in the histologically borderline cases. Corroborative evidence was a positive family history and certain laboratory tests, such as a negative stool trypsin, flat vitamin A absorption or gelatin absorption test. The duodenal intubation was performed in the majority of patients who succumbed after 1941, except in those with meconium ileus.

The autopsy protocols were examined to determine the state of nutrition at death. The gross description and the microscopic sections of the liver were reviewed in all cases satisfying the above criteria for cystic fibrosis of the pancreas. Attention was paid to the relative weight of the liver, its consistency, the presence of scarring or nodularity, as well as a variety of histologic changes, including fatty infiltration, hemosiderosis, sinusoidal congestion, periportal fibrosis, bile-duct proliferation, inspissation of biliary secretion,

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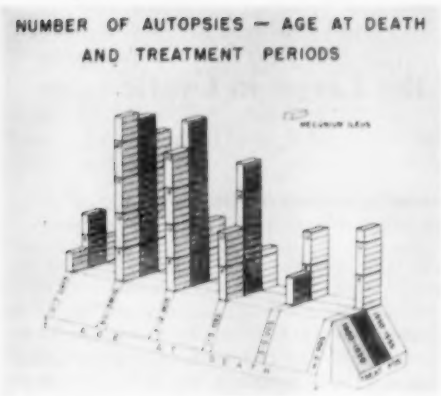
* Since this paper has been completed a more detailed analysis has been published by di Sant'Agnese, P. A., and Blanc, W. A.: A Distinctive Type of Biliary Cirrhosis of the Liver Associated with Cystic Fibrosis of the Pancreas: Recognition Through Signs of Portal Hypertension. (Pediatrics 18:387-409, 1956).



intracellular bile stasis, inflammatory changes, and shrinkage and necrosis of the liver cells.

The sections of the pancreas and the liver examined were Zenker acid fixed and were stained with hematoxylin and eosin, or toluidine blue eosin routinely, with Mallory's aniline blue and phosphotungstic acid hematoxylin stains being performed in many instances. In a few instances sections of Sudan-stained liver sections were available. A few sections were also stained with Best's carmine, Mayer's mucicarmine, or the McManus periodic-acid Schiff reaction.

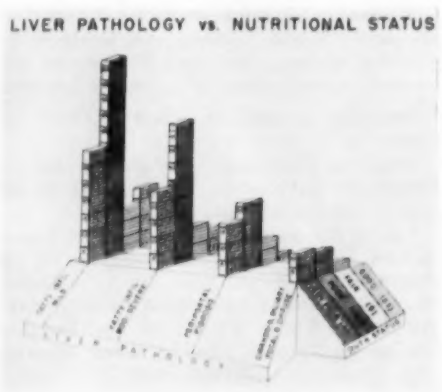
In order to determine the effects of the therapeutic regimens that have been developed in the care of this disorder and to eliminate from such consideration those infants with short life span in the meconium ileus group, the 198 cases were subdivided into four groups. The first (Group I) included those dying before 1939 when no antibiotic or pancreatic enzyme substitution was available. Group II included the cases dying during the years 1940-1949; to this group the sulfonamide compounds and penicillin were available. Group III included those cases dying between 1950-1956, when pancreatic substitution therapy, as well as the broad-spectrum antibiotics, especially chlortetracycline and oxytetracycline, were available. The same general liberal diet with a minimal restriction in fat intake plus pancreatin and a liberal vitamin intake was given to all the patients in the above groups from the time they were first treated in our clinic. The meconium ileus cases were placed in Group IV regardless of the time of death, because the usual short life of these patients in the past did not allow their course to be affected to any appreciable degree by the therapeutic procedures available.

Results

On the basis of such criteria it is interesting to note the greatly increased accuracy of diagnosis of this disease. In Group I the accuracy of diagnosis was but 3.7%; 2 cases in 54 were recognized as having the basic underlying disorder. In Group II there were 31 of 54 cases correctly diagnosed, and in Group III there were 42 of 44, or 93% correctly labeled before autopsy.

Chart 1 indicates the age of death of all cases arranged in the three periods, 1920-1939, 1940-1949, and 1950-1955. The total number of patients in each of these periods is 57, 78, and 63, respectively. One notes an increasing shift to the older age groups of children with cystic fibrosis coming to autopsy. This is also true of the meconium ileus patients, many of whom survived the initial operation for relief of the intestinal obstruction. Prior to 1940 no patient with meconium ileus survived beyond the first week of life, whereas 15 patients with meconium ileus survived beyond this age in the period 1950-1955. The percentage of cases under one year of age in the period 1920-1939 is 82%, and in the period 1940-1949 it is 70%, and in the period 1950-1955 it is 57%. Indeed, in this last group one-third of the patients died beyond the age of 3, whereas prior to 1940 no autopsy was done on a child with cystic fibrosis more than 3 years of age. These figures indicate that the autopsy population is not a homogeneous one over the years of our observation.

In Chart 2 the nutritional status is recorded at the time of autopsy. The degree



Histological Features of the Liver in Cystic Fibrosis of the Pancreas

Groups Year of autopsy	I 1920-1939	II 1940-1949	III 1950-1955	IV Meconium Ileus	Totals
Number of cases	54	54	44	46	198
Fatty infiltration					
Mild	10	10	11	12	43
Moderate to severe	23	24	29	12	88
Periportal fibrosis					
Mild	5	5	10	12	32
Moderate to marked	4	3	5	1	13
Liver-cell alteration					
Shrinkage	12	9	5	11	37
Necrosis	4	5	4	1	14
Hemosiderosis	9	3	3	11	26
Bile stasis	4	1	3	7	15
Hemosiderin in Kupffer cells	10	6	0	7	23
Accompanying liver-cell hemosiderin	3	1		6	10
Bile-duct hyperplasia	4	5	11	7	27
Focal biliary cirrhosis	3	1	6	0	10
Obstructive biliary cirrhosis	1	3	4	0	8
Congestion	28	13	13	26	80
Periportal inflammation	2	5	12	8	27
Sinusoidal inflammation	2	4	1	4	11

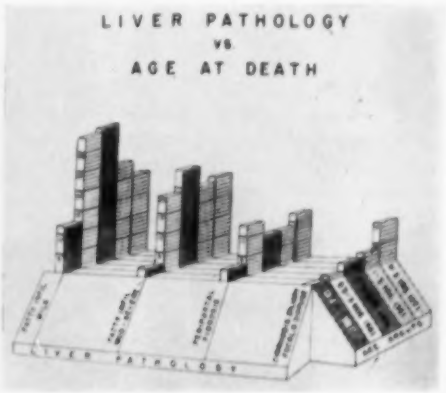
of malnutrition is judged from the amount of subcutaneous tissue, from the weight of the organs, and by the percentile weight of the child in relation to height and age. The group with the greatest degree of malnutrition was far below the 3 percentile for weight.† One notes an increasing proportion of poorly nourished children with this disease in recent years.

The histological features of the liver are listed in the Table. In this Table the patients with meconium ileus are considered separately. In Charts 2 and 3 the main histological features are plotted against the nutritional status and the age of death of the 198 patients reviewed.

Though fatty metamorphosis of a significant degree was a feature in 121 of the 198 cases, in 88 of these it was judged to be moderate to severe and easily detectable on gross examination of the liver (Figs. 1 and 2). No positive correlations could be made between the presence of fat in the liver and the general nutritional status, for a severely marasmic infant was found as frequently to have a liver with no fat as with increased fat—nor could positive correlations be made between the size of the liver and an increased liver fat content. In general, the livers of the severely marasmic infants were not significantly enlarged, even though they had a high fat content. Histologically the fat was located most frequently at the periphery of the liver lobule, though when fat infiltration was severe it was distributed equally throughout the lobule.

Of the other histological features to which attention was given, no positive correlations could be made. There appears (Chart 3) to be a tendency for a greater incidence of fatty infiltration to occur in those children with a greater duration of life.

In 45 of the 198 patients the portal triads were considered to be significantly widened,



† Accounting to the percentile weight charts of the Harvard School of Public Health, prepared by Dr. Harold C. Stuart.

Fig. 1.—The cut surface of a liver from a patient with cystic fibrosis of the pancreas, having marked fatty infiltration and a mild degree of central congestion.

owing to the presence of an increased amount of fibrous tissue (Fig. 3). This increase in fibrous tissue was never sufficient, either to distort the lobular pattern or to isolate the lobules from one another. Thus, patients having only these changes were not considered to have cirrhosis.

In more than half of the patients this increase in periportal connective tissue accompanied the obstructive and proliferative bile-duct changes discussed below, and thus in the majority the increase in peripheral fibrous tissue was considered to be related to this alteration. The alteration of periportal fibrosis alone has been noted in patients dying in the first few days of life and appears to increase slightly in the children coming to autopsy at a greater age, though this increase in part is due to the increasing appearance of the lesion of obstructive focal biliary hyperplasia. In the one-third of patients with periportal fibrosis not associated with bile-duct proliferation, only 5 of 18 cases had no fat in the liver. In six instances an inflammatory lesion was present in the portal areas and in the bile

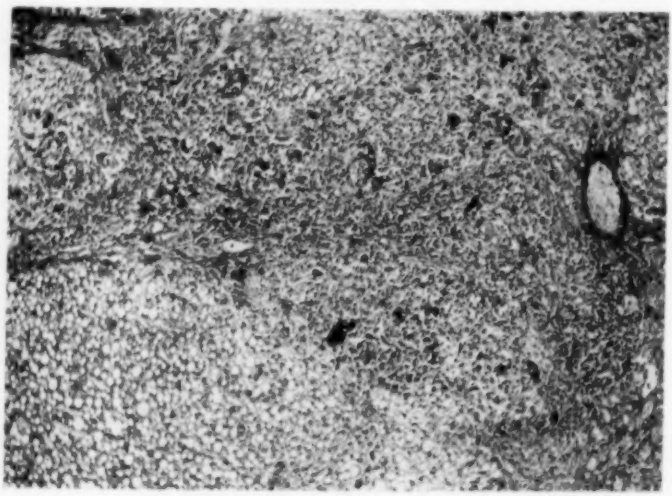


Fig. 2.—Photomicrograph of the liver of a patient, showing moderately severe degree of fatty infiltration. There is widening and inflammation of the portal triads and inspissation of the mucus secretion within the bile ducts. Hematoxylin and eosin. Mag. ×140.

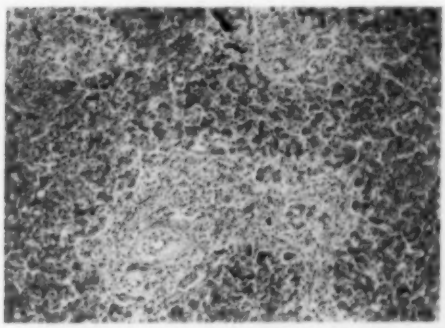


Fig. 3.—Photomicrograph. The liver shows periportal fibrosis, encroachment on the surrounding liver, a mild inflammatory response, but no bile-duct proliferation or mucus obstruction. Hematoxylin and eosin. Mag. × 110.

ducts, giving rise to a cholangitis and pericholangitis. The periportal fibrosis (Chart 3) decreased from a frequency of 30% in those whose nutrition was judged to be very poor at death to less than 10% where nutrition at autopsy was judged to be good. In the three groups over the different treatment periods, no really significant change in the frequency of this periportal fibrosis was evident, although there was a tendency for the severity of the lesion to increase in the more recently autopsied cases—again probably a reflection of the greater incidence and severity of the accompanying focal obstructive biliary hyperplasia.

Acute malnutrition may give rise to a decrease in size of the liver parenchymal cells as well as to fatty infiltration, and this change was observed to be a significant alteration in 37 of the 198 cases. In early life, especially, hemosiderosis may also be a manifestation of nutritional failure, and parenchymal hemosiderin deposits were found in 26 cases, especially frequent in Group I (Chart 1) and in Group IV, the two groups with the largest number of patients with an early death. In fully one-third of these cases the hemosiderin deposits were probably related to the low functional reserve in the liver in the immediate postnatal period. Only five children more than 6 months of age displayed this abnormality.

Hemosiderin deposits in the Kupffer cells were almost as frequent and again tended to be more prominent in the children coming to autopsy at an early age. In the meconium ileus group they were frequently accompanied by deposits of hemosiderin in the liver cells.

The most characteristic lesion of the liver in cystic fibrosis, and indeed the only one which we believe is specifically related to the inborn metabolic defect as seen in these children, was the presence of an increased number of bile ducts in the portal triads with opaque, round, eosinophilic

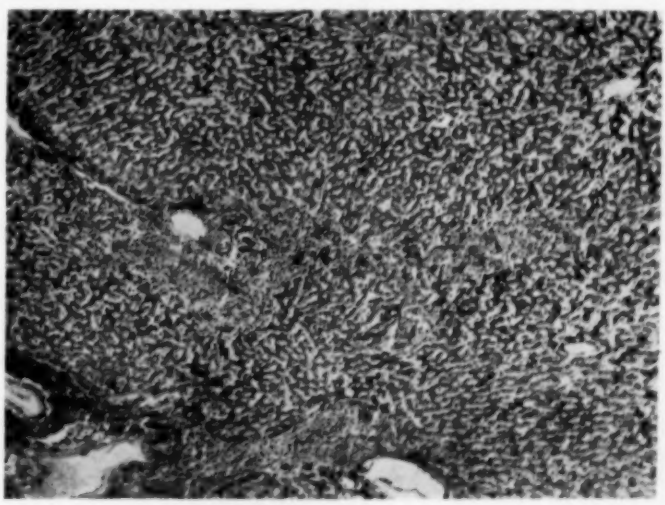


Fig. 4.—Photomicrograph. This liver shows a focal mild distortion of the lobular architecture and proliferation of bile ducts with mucus inspissation. Hematoxylin and eosin. Mag. × 85.

Fig. 5.—The inferior surface of a liver of a patient with cystic fibrosis of the pancreas in which fine focal periportal scars are present. (Same case as Fig. 4.)

masses in their lumina (Fig. 4). This substance, which had a positive McManus periodic-acid leukofuchsin stain and occasionally a positive mucicarmine stain and which did not have the same staining properties as the usual intraductal bile plug, distended the bile duct and appeared to obstruct it. Though true bile stasis within the liver parenchymal cells and Kupffer cells occurred in a total of 14 cases, nearly one-half of these were in the group with meconium ileus, and the majority of the remainder were under 6 months of age at the time of death. Here, the bile stasis was probably more closely related to hepatic-cell failure than to any obstructive effects of the abnormal staining material in the bile ducts. Such inspissated mucus plugs were found in virtually all of the 27 cases showing bile-duct proliferation. In five instances bile plugs were seen in the bile ducts, not associated with bile-duct hyperplasia or dilatation. This change, again like the bile stasis in the liver cells and Kupffer cells, was associated with liver failure and sepsis rather than any specific alteration due to pancreatic fibrosis.

Grossly, the livers in which the bile-duct hyperplasia and periportal scarring were evident were described as normal in external appearance in all but 12 cases. In these 12 the typical lesion varied from small depressed green or gray fibrous scars, often in a triangular or linear shape and tinged with a green stain, scattered irregularly over the surface of the liver, and often, most commonly, near the falciform ligament (Fig. 5), to livers in which the gross appearance approached that of a "hepar lobatum" with great depressed, often connecting scars, isolating irregular 1-4 cm. masses of normal liver tissue. In no instances were true regenerative nodules present, and the liver surfaces between the depressed scars were smooth and free of scar tissue (Figs. 6 and 9).

Thus, proliferation of the bile ducts with dilated obstructive lumens was accompanied by an increase in the periportal connective tissue, as has been noted above. As the groups of bile ducts increased in number, the areas of fibrosis increased also so that in severe cases whole low-power microscopic fields consisted of these dilated ducts lying in a dense feltwork of collagenous connective tissue (Fig. 7). These changes were striking because of the almost total absence of an accompanying inflammatory component in the uncomplicated lesions. The bile-duct hyperplasia and the periductal fibrosis were, even in the most advanced case, most characteristically a focal lesion, only scat-

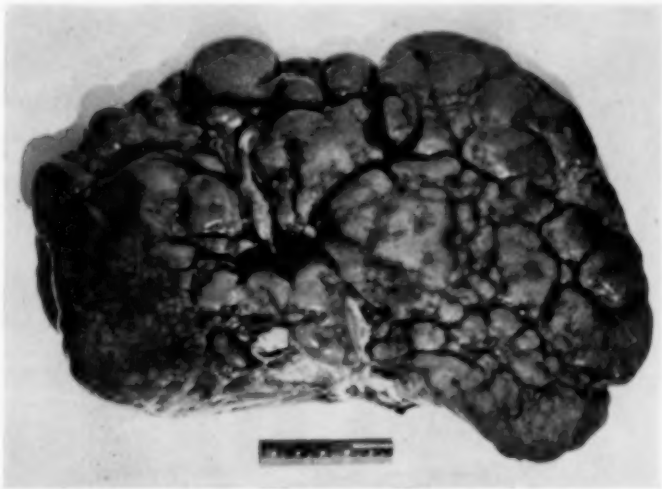


Fig. 6.—The undersurface of a liver showing deep irregular periportal scarring. Broad areas of liver uninvolved by this process are seen; no true regenerative nodules are present. (Same case as Fig. 7 and Fig. 8.)

tered portal areas being affected, the large areas of normal parenchyma lying between them (Fig. 8). Including such scattered lesions there was a total of 27 cases showing obstructive biliary hyperplasia. In nine of these the lesions were neither sufficiently frequent nor severe to give rise to lobular distortion and nodularity of the liver. Where these lesions caused isolation of one or more lobules by fibrous tissue proliferation, the designation of "focal biliary cirrhosis" was applied. Cases falling into this classification numbered 10. In the remaining eight patients with the same fundamental lesion, the gross distortion of the surface of the liver, its internal structure, and the broad fibrous tissue scars gave, we believe, a picture which could be properly called "obstructive biliary cirrhosis." However, even in these cases with broad scars and the formation of large irregular protruding masses of liver tissue there were many contiguous low-power microscopic fields of essentially normal liver. With only such focal lesions present, there was rarely evidence of either disturbance in hepatic function or increases in portal pressure.

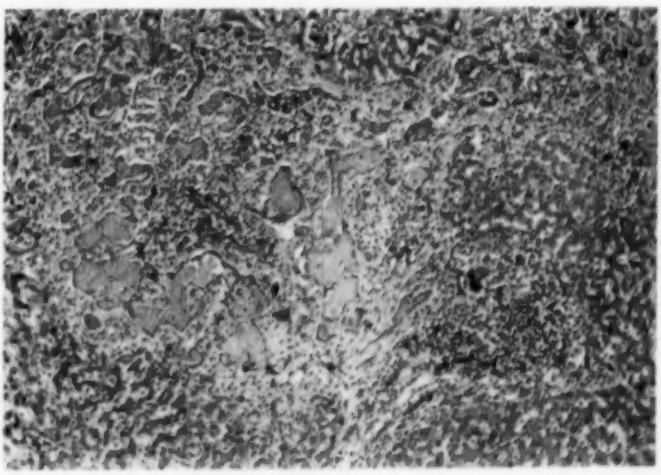


Fig. 7.—Photomicrograph. The broad scar contains proliferated bile ducts with inspissated masses of mucus accompanied by an inflammatory reaction. (Same case as Fig. 6 and Fig. 8.) Hematoxylin and eosin. Mag. ×140.

Fig. 8.—Photomicrograph. A low-power view shows the focal areas, broad scars in the lower right, and the relatively uninvolved liver of the areas in the upper left of the photomicrograph. Hematoxylin and eosin. Mag. ×17. (Same case as Fig. 6 and Fig. 7.)

Liver-function studies were carried out in 13 patients in Group III during life. These studies included cephalin flocculation tests, thymol turbidity, serum cholinesterase,[15] and determinations of one minute and total serum bilirubins. In six cases the cephalin flocculation was 3+ or more, or the thymol turbidity was more than 4 and, hence, positive. Of these six, two had no evidence of biliary hyperplasia or fibrosis at necropsy; in two the lesions were focal in character; in two cases with outspoken cirrhosis no one of the tests was positive. The serum cholinesterase was moderately to markedly depressed in all cases examined.

In 16 cases of Group III in which serum protein levels are available, these are at normal levels in all but 2; one of the latter was taken shortly before death. The gammaglobulin levels tend to be elevated above normal.

In two cases with focal or diffuse biliary cirrhosis, jaundice was present; in one of these there was an associated cholangitis; in the other the appearance of jaundice was terminal. Esophageal bleeding was not a clinical feature of any case, nor was splenic enlargement due to portal hypertension a feature of even the most advanced cases of "obstructive biliary cirrhosis." In none of these cases was the liver lesion attributable to cystic fibrosis a clinically significant one.

Fatty infiltration was present in 12 of the group of 18 having focal or well-established diffuse biliary cirrhosis, and was graded as severe in 5 of the 8 with the most advanced lesions. The lesion appeared to be commoner and severer in the older age group. The nutrition of all the 18 cases with the bile-duct proliferation in this group was noted as poor in 8 and marasmic in 9. The degree of fibrosis in this group appeared to develop *pari passu* with the proliferative bile-duct lesions. We found no cases in which other forms of cirrhosis were present in the livers of cystic fibrosis patients in this series.

Dilatation and congestion of the liver sinusoids was found in 80 of the 198 cases, a pathological change which might be considered as a manifestation of increased venous pressure due to right heart failure—yet in only 4 cases did the lesion have the characteristic features of chronic passive congestion. In the majority the dilatation was thought to be due in part to shrinkage of the liver-cell cords due to loss of substance in the liver-cell parenchyma, rather than passive congestion.

Focal necrosis of liver cells was found in 19 cases, periportal inflammation in 27, and lobular and sinusoidal inflammation in 11 cases. None of these lesions are considered to be specific for cystic fibrosis and are probably, except in a few cases of periportal inflammation, terminal in nature. None of the lesions could be shown to have any significant correlations with either the clinical course or the other pathological features in the liver.

Comment

The constantly increasing duration of life in the children with cystic fibrosis of the pancreas will, as has been shown, give a constantly changing pathological picture at the postmortem table. Moreover, the recognition of cases with partial syndromes of the metabolic disorder will also give rise to variants in the morphological appearance.

Fatty metamorphosis of the liver is one of the most constant features of the disease, yet a nonspecific one, and is difficult of interpretation. Although clinically these children have livers that are frequently easily palpable below the costal margin, the postmortem data show that they are not enlarged, even when heavily infiltrated with fat. Since the livers are actually not significantly enlarged, which would be expected to occur if the fatty infiltration were of long duration, it can be suspected that the fatty infiltration is a terminal affair of a few days' or weeks' duration. The marked emphysema and downward displacement of the diaphragm that these children have accounts for their palpable livers. Thus, the liver changes cannot easily be compared with the changes in fatty livers of tropical protein deficiency. The adequate serum-protein levels demonstrated indicate that the fat deposition is not a change secondary to protein deficiency. It must be admitted that the growth patterns of these children are abnormal, especially if life is unprotected by antibiotic therapy and also in the last years of life when the terminal state is prolonged. This might indicate a protein deficiency but is much more likely to be secondary to infection rather than a specific nutritional deficiency.

Not only in experimental animals but also in humans alterations in the liver with fatty infiltration and periportal fibrosis have been described after ablation or destruction of the pancreas secondary to pancreatic lithiasis.[16-18] In each instance, however, these pancreatic changes are frequently complicated—in dogs by the diabetic state and in humans by diabetes and alcoholism, which may by themselves induce fatty metamorphosis of the liver.

Chronic pulmonary infection, especially tuberculosis, has been reported to give rise to fatty metamorphosis of the liver.[19-20] The relation of the well-known, severely destructive pulmonary suppurative lesions in cystic fibrosis of the pancreas to fatty infiltration must be purely speculative.

Chlortetracycline and oxytetracycline, experimentally and in humans, have been shown to alter liver morphology and induce fatty infiltration.[21-23] It is obvious, however, that the exhibition of such antibiotics can play only a partial role here, since fatty changes were present before these drugs became available.

The increasing percentage of patients dying with fatty infiltration of the liver in cystic fibrosis of the pancreas might be ascribed to their longevity and the prolonged stages of their terminal illness. However, it offers a definite challenge as to its causation and cure.

The fibrosis of the periportal areas of the liver in cystic fibrosis of the pancreas

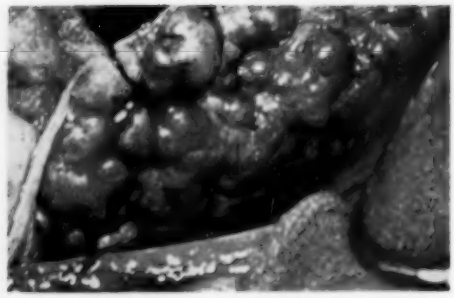


Fig. 9.—Photograph of the liver at operation of a patient with cystic fibrosis of the pancreas and portal hypertension. There is marked irregularity of the surface, punctuated by deep scars and large masses of intervening liver. (Same case as Fig. 10 and Fig. 11.)

appears to have two distinct etiologies. The commonest and most easily understood origin has to do with the focal obstructive biliary changes secondary to plugging of the bile ducts with the mucus-bile plugs which have been described. Occasionally, such changes may be associated with a cholangitis or pericholangitis with a more rapid deposition of fibrous tissue. Of much more difficult interpretation is the periportal fibrosis which is found in the absence of the obstructive biliary cirrhosis. This lesion may be associated with considerable fatty infiltration, yet more frequently it stands alone. It does not appear to keep pace with the increasing tendency for fatty infiltration in the older groups when unaccompanied by obstructive biliary hyperplasia. Such an alteration may be secondary to liver-cell necrosis, periportal inflammation, or fatty infiltration of the liver cells. We have evidence only of the latter two in our series. Fatty infiltration secondary to dietary inadequacy gives rise to significant portal fibrosis in children only after a prolonged course. We have found no cases of cirrhosis in cystic fibrosis without the obstructive proliferative biliary lesions. This appears to be contrary to the experience of others who are able to present cases of what appears to be a post-necrotic scarring and Laennec's cirrhosis with portal hypertension in cystic fibrosis of the pancreas. From the photomicrographs the cases of Webster,[10] previously reported by Pitt,[9] appear to fall into the obstructive biliary group rather than the latter category.

As we have pointed out above, even with marked gross distortion of the liver the hepatic function is usually unimpaired and portal obstruction develops only rarely.

Of the autopsied cases none had a history of esophageal varices, hematemesis, or melena. Of interest is the recent report of di Sant'Agnese, in which 7 of 311 patients with cystic fibrosis of the pancreas had portal hypertension.[13] In this series patients with cystic fibrosis of the pancreas as the underlying disorder constituted a large percentage of all patients with a chief complaint of portal hypertension. This has not been our experience, for among 600 patients with cystic fibrosis we have had but a single patient with clinical portal hypertension and of 43 cases of portal hypertension recently summarized by Hsia and Gellis,[24] from this institution, no cases had such an underlying disorder. This single case is of interest because the changes in the liver are not the typical ones seen in cystic fibrosis of the pancreas.

This boy's disease began while a newborn, with large and bulky stools, followed at 2 months of age by his first severe respiratory illness and at 1½ years by a prolapse of the rectum. The diagnosis of cystic fibrosis of the pancreas was not established until the age of 10 years. His first bleeding episode took place at the age of 12½ years, and a second occurred at 14½ years. The liver function tests were negative except for a cephalin flocculation of 3-4+. A splenectomy and splenorenal shunt and pancreatic and liver biopsies were performed. The liver at operation (Fig. 9) had the large irregular nodular appearance with broad contracted scars seen in advanced cases of liver involvement with cystic fibrosis of the pancreas. Microscopically, though there was marked alteration of the lobular pattern in focal areas and no evidence of lobular regeneration (Fig. 10), there was none of the marked proliferation of the bile ducts with inspissated mucus (Fig. 11) seen in the majority of our cases of liver involvement with this disorder.

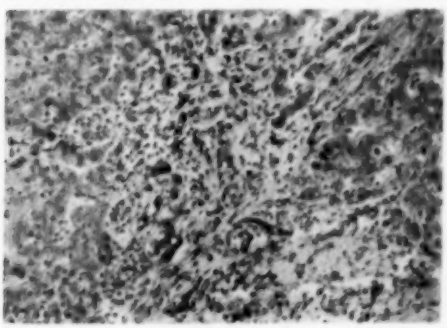
This latter feature has also been seen in those cases reported by di Sant' Agnese.[13] These cases, then, may represent one of three theoretical possibilities: (1) They are

Fig. 10. — Photomicrograph. There are broad periportal scars and lobular alterations in pattern, but no proliferated bile ducts or inspissated mucous materials. No regenerated nodules are present. Toluidine blue, eosin. Mag. × 35.

a variant of the usual alteration in cystic fibrosis; (2) they are an end-stage of the usual process seen in cystic fibrosis in which the proliferated bile ducts may have atrophied and disappeared, as has been seen in long-standing cases of biliary cirrhosis due to absence of the extrahepatic ducts,[25] or (3) the focal changes seen in the limited biopsy specimen are the result of an intermittent obstruction due to the inspissated mucus plugs deep within the liver substance, and these plugs do not appear in the material examined at biopsy. Thus the changes would represent a focal biliary cirrhosis due to a segmental obstruction in the biliary system with a subsequent subsidence, scarring, and healing of the local lesions.

Occasionally, jaundice may be present, but this is usually in very young infants in whom immaturity of the liver is present, or in cases where a cholangitis or pericholangitis is present.[26] It is a striking feature that even though the bile ducts draining a lobule are plugged with inspissated bile material, bile stasis within that lobe is not seen in the liver cells or canaliculi drained by these bile ducts. It is interesting that the obstruction of the hepatic or common ducts by mucus plugs does not occur, since obstruction and almost a complete obliteration of both cystic duct and gallbladder is not an uncommon event.

Fig. 11.—Photomicrograph. A view of one portal triad in the liver shown in Figures 9 and 10 to show the absence of proliferated bile ducts or inspissated mucous material. A mild subacute inflammatory reaction is present. Toluidine blue, eosin. Mag. × 250.



Summary

The gross and microscopic findings of the liver in 198 autopsied cases of cystic fibrosis of the pancreas were reviewed. The increasing age of autopsied patients with this disease and the changes in therapy over the years from 1920-1955 gave a nonhomogeneous picture. The most frequent finding was that of fatty infiltration, occurring in 130 patients. Periportal fibrosis was found in 45 cases, but in 27 of these it was associated with hyperplasia of the bile ducts. The latter lesion gave rise to a focal biliary cirrhosis in nine instances, and a

diffuse biliary cirrhosis in eight. Periportal fibrosis alone was never sufficiently extreme to be labeled cirrhosis. In no instance in the patients who came to autopsy did the biliary cirrhosis lead either to liver failure or to clinical portal hypertension. One clinical case of cirrhosis, portal hypertension, and esophageal varices has been seen. Alterations in liver-cell architecture were found in one-third of the cases, and these consisted of shrinkage, hemosiderosis, bile stasis, and necrobiosis. Congestion was a finding in 80 cases, but only rarely could it be ascribed to right-sided heart failure. Periportal and sinusoidal inflammation were found in 27 and 11 instances, respectively.

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REFERENCES

1. Andersen, D. H.: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease: Clinical and Pathologic Study, Am. J. Dis. Child. 56:344, 1938.

2. Farber, S.: Pancreatic Insufficiency and the Celiac Syndrome, New England J. Med. 229:653, 1943.

3. Farber, S.: Pancreatic Function and Disease in Early Life: V. Pathologic Changes Associated with Pancreatic Insufficiency in Early Life, Arch. Path. 37:238, 1944.

4. Baggenstoss, A. H., and Kennedy, R. L. J.: Fibrocystic Disease of the Pancreas: A Study of 14 Cases, Am. J. Clin. Path. 15:64, 1945.

5. Wigglesworth, F. W.: Fibrocystic Disease of the Pancreas, Am. J. M. Sc. 212:351, 1946.

6. Zuelzer, W. W., and Newton, W. A., Jr.: The Pathogenesis of Fibrocystic Disease of the Pancreas: A Study of 36 Cases with Special Reference to the Pulmonary Lesions, Pediatrics 4:53, 1949.

7. Bostick, W. L., and Rinehart, J. F.: Pathologic Lesions in Cystic Fibrosis of the Pancreas, J. Pediat. 37:469, 1950.

8. Pugsley, H. E., and Spence, P. M.: A Case of Cystic Fibrosis of the Pancreas Associated with Chronic Pulmonary Disease and Cirrhosis of the Liver, Ann. Int. Med. 30:1262, 1949.

9. Pitt, D.: Fibrocystic Disease of the Pancreas: A Review of 14 Cases, M. J. Australia 1:91, 1948.

10. Webster, R., and Williams, H.: Hepatic Cirrhosis Associated with Fibrocystic Disease of the Pancreas: Clinical and Pathological Reports of 5 Patients, Arch. Dis. Childhood 28:343, 1953.

11. Fibrocystic Disease of the Pancreas: A Congenital Disorder of Mucus Production—Mucosis, Edited by Martin Bodian, New York, Grune & Stratton, Inc., 1953.

12. May, C. C.: Cystic Fibrosis of the Pancreas in Infants and Children, American Lecture Series 235, Springfield, Ill., Charles C Thomas, Publisher, 1954.

13. di Sant' Agnese, P. A.: Fibrocystic Disease of the Pancreas with Cirrhosis of the Liver, in Fibrocystic Disease of the Pancreas, 18th Ross Pediatric Research Conference, Columbus, 1956, p. 92.

14. Shwachman, H.; Pryles, C. V., and Gross, R. E.: Meconium Ileus: A Clinical Study of 20 Surviving Patients, A. M. A. J. Dis. Child. 91:223, 1956.

15. Bleisch, V. R., and Shwachman, H.: Serum Cholinesterase Values in Childhood in Health and Disease, Pediatrics 13:426, 1954.

16. Chaikoff, I. L.; Connor, C. L., and Biskind, G. R.: Fatty Infiltration and Cirrhosis of the Liver in Depancreatized Dogs Maintained with Insulin, Am. J. Path., 14:101, 1938.

17. Best, C. H.: Diabetes, Insulin and the Lipotropic Factors, American Lectures in Physiology, Springfield, Ill., Charles C Thomas, Publisher, 1948.

18. Sanes, S.; Miller, D. K.; Brason, F. W., and Geist, O. B.: Fatty Change and Cirrhosis of the Liver in Patients with Pancreatic Lithiasis, Arch. Int. Med. 85:980, 1950.

19. Saphir, O.: Changes in the Liver and in the Pancreas in Chronic Pulmonary Tuberculosis, with Special Reference to Islets of Langerhans, Arch. Path. 7:1026, 1929.

20. Jones, J. M., and Peck, W. M.: Incidence of Fatty Liver in Tuberculosis with Special Reference to Tuberculous Enteritis, Arch. Int. Med. 74:371, 1944.

21. Sborov, V. M., and Sutherland, D. A.: Fatty Liver Following Aureomycin and Terramycin in Chronic Hepatic Disease, Gastroenterology 18:598, 1951.

22. Lepper, M. H.; Wolfe, C. K.; Zimmerman, H. J.; Caldwell, E. R., Jr.; Spies, H. W., and Dowling, H. F.: Effect of Large Doses of Aureomycin on Human Liver, A. M. A. Arch. Int. Med. 88:271, 1951.

23. Yesner, R., and Kunkel, P.: Preliminary Observations on the Effect of Aureomycin, Ter-

ramycin, Tibione, Combined Tibione and Streptomycin, and Chloromycetin on the Morphology of the Liver in Man, Yale J. Biol. & Med. 23:299, 1950.

24. Hsia, D. Y., and Gellis, S. S.: Portal Hypertension in Infants and Children, A. M. A. Am. J. Dis. Child. 90:290, 1955.

25. Craig, J. M.; Gellis, S. S., and Hsia, D. Y.: Cirrhosis of the Liver in Infants and Children, A. M. A. Am. J. Dis. Child. 90:299, 1955.

26. Gatzimos, C. D., and Jowitt, R. H.: Jaundice in Mucoviscidosis (Fibrocystic Disease of Pancreas): Report of 4 Cases, A. M. A. Am. J. Dis. Child. 89:182, 1955.

Oral Sulfonamides in Lipid Emulsion

A Comparative Study of Free Sulfonamide Levels in Blood Following Oral Administration of Sulfonamides in Aqueous Suspension and in Lipid Emulsions to Infants and Children

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Feinstone [1] in 1940 called attention to the fact that following the oral administration of sulfonamides in lipid emulsion more sustained blood levels of free sulfonamide were obtained. Peterson and Finland [2] in 1942 observed that patients given oral sulfonamides after meals had consistently higher blood levels than when the same dose was given in a fasting state. In 1945 Reinhold [3] confirmed Peterson's observations and suggested the clinical use of lipid emulsions as vehicles for sulfonamide administration. No practical application of these observations was made until recently, when lipid emulsions of acetyl sulfisoxazole, sulfadiazine, and a triple sulfonamide were prepared.

The present report is a comparative evaluation of the blood level of free sulfonamide obtained after the oral administration to fasting subjects of three sulfonamide preparations: (1) standard aqueous suspension, (2) a lipid emulsion base, and (3) in a limited number of patients the standard aqueous suspension followed by a meal which included milk.

Material and Methods

Studies were carried out in 92 children ranging in age from 2 weeks to 15 years, all of whom were convalescent at the time of study. Each patient served as his own control receiving the sulfonamide in both the aqueous suspension and in a lipid emulsion base of absorbable fat with a three- to seven-day interval between studies (control blood specimens were obtained before each study). An oral dose of 70 mg. per kilogram of body weight was used throughout. Care was taken to be certain that all the prescribed dose was taken and none regurgitated. For the single-dose studies the medication was given in the fasting state, and no food was offered until six hours later, except in those patients in whom the influence of diet was being evaluated. In this latter group a diet for age including milk was administered immediately after the sulfonamide. In the multiple-dose studies feedings were given on the usual ward schedule.

Blood specimens for analysis were drawn prior to sulfonamide administration, and at 1-, 2-, 4-, 6-, 8-, and 24-hour intervals in the single-dose studies. In the multiple-dose studies specimens were taken prior to drug administration and at 1, 4, 7, and 11 hours following medication. The free sulfonamide level in the blood was determined by the capillary method of Bratton and Marshall.[4] A standard curve was prepared for each sulfonamide preparation utilized and the results expressed as milligrams of free sulfonamide per 100 ml. whole blood.

Acetyl sulfisoxazole was supplied in a vanilla-flavored aqueous suspension (Gantrisin Acetyl, Hoffman-La Roche) and as a mint-flavored lipid emulsion (Lipo Gantrisin Acetyl, Hoffman-La Roche) each containing the molecular equivalent of 500 mg. of sulfisoxazole per 5 cc. (actually 593 mg. of acetyl sulfisoxazole per 5 cc.). The sulfadiazine used was either in an orange-flavored aqueous suspension or a strawberry-flavored lipid emulsion base (Lipo-Diazine, Donley Evans), each containing 500 mg. of sulfonamide per 5 cc. The triple sulfonamides contained 500 mg. of sulfonamide per 5 cc. as 167 mg. sulfadiazine, 167 mg. of sulfamerazine, and 167 mg. sulfamethazine in either an aqueous suspension or lipid emulsion (Lipo-Triazine, Donley Evans).

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From the Departments of Pediatrics and Internal Medicine Baylor University College of Medicine, the Ben Taub Infectious Disease Laboratory, and the Jefferson Davis City-County Hospital.

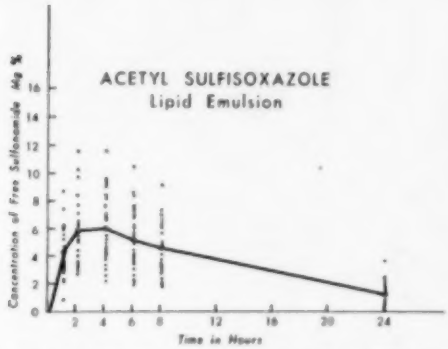

Fig. 1.—Following a single oral dose of 70 mg. per kilogram of body weight of acetyl sulfisoxazole in lipid emulsion, a peak level is reached by the 2nd hour and effective levels are still present by the 12th hour after medication.

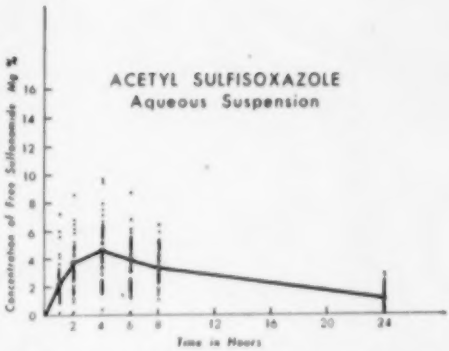

Fig. 2.—A similar dose of 70 mg. per kilogram of acetyl sulfisoxazole in aqueous suspension administered in the fasting state does not show a peak level until the fourth hour, and the maximum average level is almost 50% less than that noted in Figure 1.

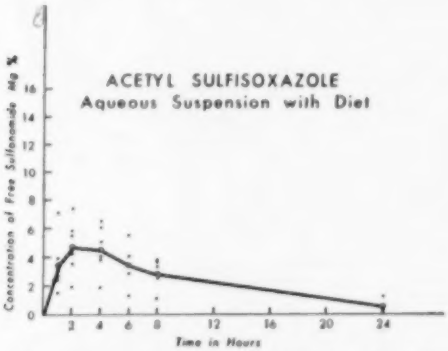

Fig. 3.—A diet containing milk given immediately after a single oral dose of acetyl sulfisoxazole in aqueous suspension shows a more rapid absorption peak than was obtained in Figure 2 but is otherwise not different and definitely does not achieve the absorption seen in Figure 1.

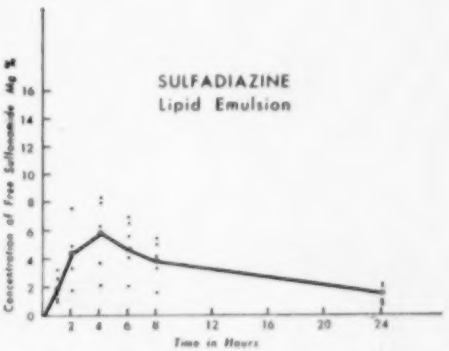

Fig. 4.—Sulfadiazine in a single oral dose of 70 mg. per kilogram in a lipid emulsion shows rapid absorption with a peak at four hours.

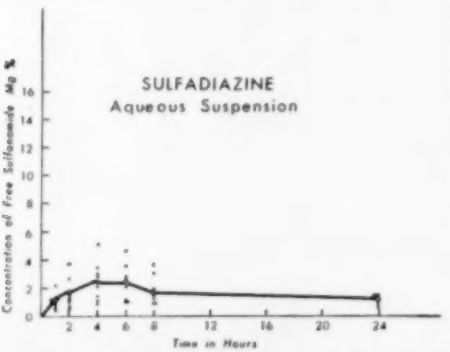

Fig. 5.—Oral sulfadiazine in the standard aqueous suspension given in a fasting state was poorly absorbed by comparison with the lipid emulsion form in Figure 4.

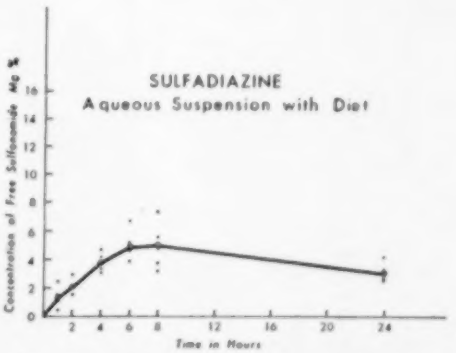

Fig. 6.—A diet containing milk clearly improved the absorption of aqueous sulfadiazine producing a peak at six hours comparable with that of the lipid emulsion form.

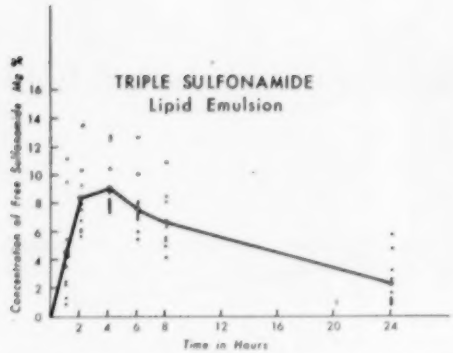

Fig. 7.—A triple sulfonamide in a lipid emulsion vehicle given as a single oral dose showed rapid absorption and sustained blood levels.

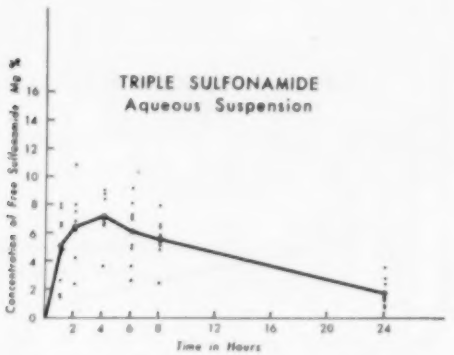

Fig. 8.—The same triple sulfonamides in the fasting state and in a similar dose but using the standard aqueous suspension shows equally rapid absorption but a lower peak when compared with the lipid emulsion of Figure 7.

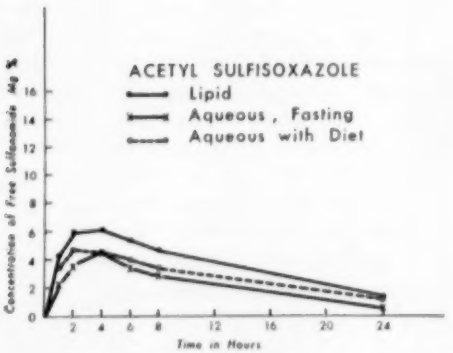

Fig. 9.—A composite graph of the average values for the three studies with acetyl sulfisoxazole to facilitate comparison.

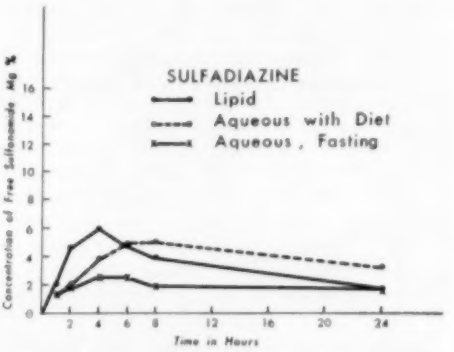

Fig. 10.—A composite graph of the average values for the sulfadiazine studies.

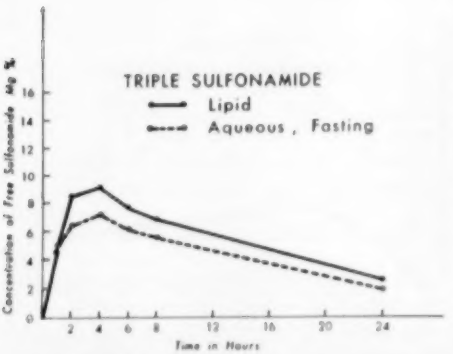

Fig. 11.—The average values graph for the two studies of the absorption of triple sulfonamide.

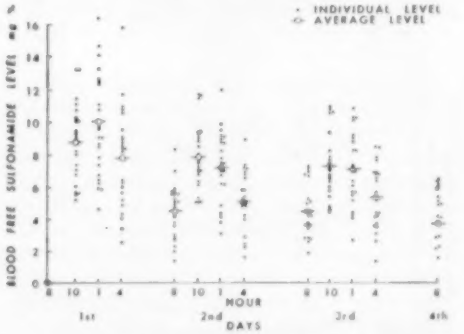

Fig. 12.—Results of a multiple oral dose trial of the lipid emulsion of acetyl sulfisoxazole. Each patient was given 140 mg. per kilogram initially followed by 70 mg. per kilogram every 12 hours at 9 a.m. and 9 p.m. for 4 days. The 23 children studied ranged in age from 1-13 years and in weight from 10-37 kg.

Results and Comment

Figure 1 illustrates the mean and range of values obtained after the administration of a single oral dose of acetyl sulfisoxazole in a lipid emulsion base to 30 infants and children. Free sulfonamide appeared at the one-hour interval in all patients studied, reached a peak at two hours, and remained up through the eight-hour interval. The absorption of a similar dose of acetyl sulfisoxazole in aqueous suspension in the fasting state is shown in Figure 2. Although the shape of the curve is similar, the level at one hour is approximately one-half that obtained with the lipid emulsion preparation and a peak value is not reached until the fourth hour. This level is less than that seen with the lipid emulsion form. The administration of a single dose of an aqueous suspension of acetyl sulfisoxazole followed by normal diet for age which included milk is shown in Figure 3. It will be seen that the rate of absorption in these subjects is somewhat greater than that of the fasting subjects receiving the aqueous suspension but less than that of the children who received the lipid emulsion form.

A similar study was carried out with sulfadiazine. Figure 4 illustrates the rapid appearance of sulfadiazine in the blood following the administration of a single dose of sulfadiazine in a lipid emulsion. A peak level was reached by the fourth hour. By contrast, an aqueous sulfadiazine suspension produced a peak at four hours of less than one-half (Fig. 5) that of the lipid emulsion of sulfadiazine. The administration of aqueous sulfadiazine suspension followed by a diet containing milk produced a delayed peak of absorption at 6 hours but a sustained blood level that surpassed that of the lipid emulsion at the 8- and 24-hour intervals (Fig. 6).

A single oral dose of a triple sulfonamide preparation in lipid emulsion was followed by a rapid rise in blood sulfonamide level with a peak at four hours (Fig. 7). The same triple sulfonamides combination in aqueous suspension produced a similar shaped curve of absorption, but the peak value was approximately 20% lower (Fig. 8).

The prolonged blood levels of free sulfonamide attained after administration of single oral doses of various sulfonamides in lipid emulsion vehicles led us to investigate a multiple-dose schedule. After preliminary trials a schedule consisting of an initial loading dose of 140 mg. per kilogram followed by 70 mg. per kilogram every 12 hours was studied and found to produce sustained blood levels. The average blood level and the range in 23 infants and children studied are shown in Figure 12. The generally higher blood levels during the first day as a result of the loading dose are followed by somewhat lower but more consistent levels on the second and third days of therapy. These data suggest that a 12-hour dosage schedule of a lipid suspension of acetyl sulfisoxazole should be an effective therapeutic scheme.

Conclusions

The absorption of sulfonamides administered orally in a lipid emulsion vehicle appears to be consistently more rapid and more complete than when the same sulfonamide is given in aqueous suspension. This is illustrated in the composite graphs of the mean values (Fig. 9-11) for the individual studies. The administration of a diet following a dose of sulfonamide in aqueous suspension improves the rapidity and degree of sulfonamide absorption.

The absorption of orally administered sulfonamides in a lipid emulsion, as measured by the blood level of free sulfonamide, is more rapid and usually greater than that attained when aqueous suspensions of sulfonamide are administered with a diet including milk. In the patients studied a multiple oral dosage schedule using acetyl sulfisoxazole in a lipid emulsion of an initial loading dose of 140 mg. per kilogram followed by 70 mg. per kilogram every

12 hours provides average blood levels of free sulfonamide in the range of 3.8-10.0 mg. per 100 cc.

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REFERENCES

1. Feinstone, W. H.; Wolff, R., and Williams, R. D.: Experimental Chemotherapeutic Studies upon a Series of N-Acyl Derivatives of Sulfonilamide, J. Bact. 39:47, 1940.

2. Peterson, O. L., and Finland, M.: Effect of Food and Alkali on Absorption and Excretion of Sulfonamide Drugs After Oral and Duodenal Administration, Am. J. M. Sc. 204:581, 1942.

3. Reinhold, J. G.; Phillips, F. J., and Flippin, H. F.: Comparison of Behavior of Microcrystalline Sulfadiazine with That of Ordinary Sulfadiazine in Man, Am. J. M. Sc. 210:141, 1945.

4. Bray, W. E.: Synopsis of Clinical Laboratory Methods, St. Louis, C. V. Mosby Company, 1949, p. 445.

A Study of Hemophilia

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It is now possible to distinguish several disorders of blood coagulation within the condition previously designated as hemophilia, and to identify each as being characterized by defective production of thromboplastin. Whether the latter results from a quantitative deficiency in one of several substances or from the presence of an inhibitor of that substance is debated. Matters of terminology also remain unsettled, and the status of still other hemophilia-like disorders awaits confirmation. At present, though, three forms of hemophilia are commonly recognized and usually designated antihemophilic globulin (AHG) deficiency, plasma thromboplastin component (PTC) deficiency, or plasma thromboplastin antecedent (PTA) deficiency.[1] It is generally agreed that differentiation of these disorders on clinical grounds alone is virtually impossible and that definitive diagnosis, and to a certain extent rational therapy, rests on the results of certain laboratory tests.

In the light of these findings the present study was undertaken to reevaluate those patients admitted to this hospital with the diagnosis of hemophilia. The results indicate a higher incidence of PTC deficiency and of so-called circulating anticoagulants than was expected on the basis of other reports. Instances of multiple deficiencies are also reported. The value of the thromboplastin generation test as a diagnostic method is again emphasized.

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Materials and Methods

Thirty-two patients who had been admitted to this hospital from 1940 through 1955 with a diagnosis of hemophilia comprise the material for this study. All were male, and all but one were white; Patient 6 was Negro. They ranged in age from 2 months to 17 years. Patients 2 and 5 and Patients 13 and 18 were brothers; Patients 23 and 25 were cousins.

The coagulation time, bleeding time, platelet count, and plasma prothrombin times were determined by the methods of Lee-White,[2] Duke,[3] Dameshek,[4] and Quick,[5] respectively. Serum prothrombin time was measured by the method of Stefanini,[6] employing a solution of $BaSO_4$ (0.15M) to prepare "$BaSO_4$ plasma."

Siliconized syringes were used for venipunctures, and sodium oxalate (0.1M) served as anticoagulant.

The hemophilias were differentiated on the basis of results of either one or both of the following procedures:

A. *Differential Mixtures.*—In this test one measures the ability of various plasma and sera to correct a patient's coagulation defect. The patient's freshly drawn blood was added in 1.9 ml. amounts to tubes containing 0.1 ml. of one of the various blood derivatives. The serum prothrombin time was measured after 60 minutes incubation at 37 C. The blood derivatives employed and the interpretation of results were those in common usage, as shown in Table 1. For practical purposes fresh normal $BaSO_4$ plasma contains AHG and PTA but not PTC, while serum provides PTC and PTA but not AHG.

B. *The Thromboplastin Generation Test.*—This test[7] was modified to the extent that sodium oxalate (0.1M) rather than citrate was used as anticoagulant and barium sulfate (0.15M) rather than aluminum hydroxide was used to adsorb prothrombin and the "serum" factors. In this test a potent thromboplastin, whose activity can be measured against a normal plasma substrate, is produced by a mixture of normal platelets, serum, and deprothrombinized (i. e., $BaSO_4$ treated) plasma. In 25 normal subjects studied the thromboplastin so prepared caused clotting of normal plasma in 7 to 15 seconds (average 10.5 seconds). By substituting

TABLE 1.—*Effect of Normal and Deficient Blood Derivatives on the Coagulation Defect of AHG, PTC, and PTA Deficient Patients*

Deficiency of	Fresh Normal Plasma	Fresh Normal $BaSO_4$ Plasma	Normal Serum 48 Hr. or More Old	Plasma from Known AHG Deficiency	Plasma from Known PTC Deficiency
AHG	+	+	−	−	+
PTC	+	−	+	+	−
PTA	+	+	+	+	+

Correction of prolonged coagulation time and/or reduced prothrombin consumption indicated by +, lack of correction by −.

a patient's platelets, serum, or deprothrombinized plasma into an otherwise normal system, it is possible with this technique to evaluate the role of each in the generation of thromboplastin. The serum acts primarily as a source of PTC, PTA, and factor VII, while the deprothrombinized plasma provides AHG, PTA, and factor V. In the absence of a prolonged plasma prothrombin time, the finding of poor thromboplastin production using the patient's serum in an otherwise normal system indicates PTC deficiency and poor production using the patient's deprothrombinized plasma indicates AHG deficiency; in PTA deficiency normal thromboplastin generation occurs when either the patient's plasma or his serum is used alone in an otherwise normal system, but poor generation results when both the patient's plasma and serum are used in the generation mixture.[8]

Results

The clinical features were of no help in the differential diagnosis, and, since they add little to the observations of others, only a brief summary will be given. Thus in this group of patients both mild and severe forms of AHG and PTC deficiency were encountered; bleeding began before the age of 2 years in 90% of both AHG and PTC deficiency children; hemarthroses were as frequent a cause of hospitalization in PTC deficient as in AHG deficient patients and occurred in both groups usually after 3 years of age; mouth hemorrhages were equally common in the two groups prior to age 3 years; a family history suggesting a sex-linked recessive mode of inheritance was positive in approximately two-thirds of both groups; the pattern of severity of hemorrhagic manifestations seemed to remain essentially unchanged from one generation to another in the same family.

PTC Deficiency.—Nine patients, or 28% of the total, were found to have this type of hemophilia.

The results of coagulation tests performed on these are listed in Table 2. Since more than one set of observations was made in all but Patients 3 and 7, representative values are given.

The coagulation time was definitely prolonged in only four subjects, being normal (6-14 minutes) in three and only slightly prolonged in two others. The serum prothrombin time was abnormally short in eight of the patients but was within normal limits (greater than 20 seconds) for Patient 9.

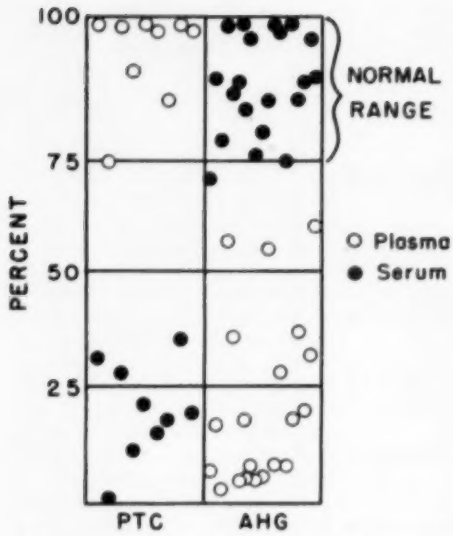
In Table 2 serum prothrombin values of the "differential mixtures" are given in seconds in columns 3 through 8, and in per cent prothrombin consumption in columns 9 through 14. It is apparent from these values that a satisfactory diagnosis often cannot be reached with this technique. Thus, only four patients (2, 3, 6, and 8) exhibited "typical patterns." There was greater effect than anticipated with $BaSO_4$ treated plasma in Patients 1, 4, and 5 and likewise a greater effect than anticipated with PTC deficient plasma in Patients 1, 4, 5, and 7. In view of results of the thromboplastin generation test, it seems unlikely that these latter patients have PTA rather than PTC deficiency. One of the patients (5) whose pattern was equivocal is the brother of Patient 2, in all respects typical of PTC deficiency.

Results of the thromboplastin generation test were clear-cut. The serum of every patient when substituted in an otherwise normal system failed to generate thromboplastin normally (ranging from 1% to

TABLE 2.—*Summary of Coagulation Tests in PTC Deficient Patients*

Patient	Coag. Time,	Serum Prothrombin, Seconds						Prothrombin Consumption, %						Thromboplastin Generation			
		After Addition of*						After Addition of*						Plasma†		Serum†	
	Min.	Alone	N.P.	BaS	Ser.	AHG	PTC	Alone	N.P.	BaS	Ser.	AHG	PTC	Sec.	%	Sec.	%
1	13.5	12.4	31.8	17.0	25.3	34.6	14.4	6	95	70	91	96	48	8.2	>100	24.0	32
2	25	13.0	54.2	14.0	25.0	62.5	12.6	15	97	40	90	98	8	15.0	73	64.2	1
3	>60	13.0	45.5	14.7	90.0	85.0	—	15	96	52	99	99	—	7.3	>100	24.8	28
4	>60	13.0	59.0	17.6	62.0	48.0	18.6	15	97	75	98	97	79	11.0	93	36.2	12
5	38	14.8	54.0	17.0	65.8	51.0	17.0	53	97	70	98	97	70	9.7	>100	28.3	21
6	7	15.4	22.0	15.9	47.1	54.8	16.0	58	87	62	97	97	63	9.6	>100	33.1	15
7	17	15.7	23.0	—	>180.0	27.0	18.3	60	88	—	99	93	78	12.1	87	29.8	18
8	14	17.2	32.9	17.5	89.9	53.5	16.8	72	95	74	99	97	68	9.0	>100	23.0	35
9	17	21.7	24.0	25.2	44.0	19.0	21.0	86	89	91	96	81	85	8.8	>100	29.2	19

* For interpretation of abbreviations see Table 1.
† Indicates maximal activity of patient's $BaSO_4$ plasma or serum when substituted singly in an otherwise normal system in the thromboplastin generation test.



The generation of thromboplastin in per cent in AHG and PTC deficiency when patient's plasma or serum is substituted singly in an otherwise normal system.

35%), while the patient's plasma when so substituted did not differ significantly from the normal (ranging from 73% to greater than 100%). The data in Table 2 indicate maximal thromboplastic activity for serum and plasma, obtained from four-nine minutes and from three-five minutes, respectively, after completion of the incubation mixture. Results of this test in PTC deficiency are also shown graphically in the Figure and compared with the findings in AHG deficiency.

Plasma prothrombin times were normal in each patient.

Bleeding times greater than seven minutes were recorded in two of the nine patients.

All three of the patients (2, 4, and 5) whose disease was considered clinically to be of moderate to marked severity exhibited long clotting times and poor prothrombin consumption. Thromboplastin generation was distinctly less in two of these (Patients 2 and 4) than in the remainder of the PTC group. Except for Patient 3, whose clinical severity at 10 months of age was difficult to assess, the rest were felt to have mild to moderately severe hemorrhagic manifestations. Their coagulation times were either normal or nearly so, but serum prothrombin and thromboplastin generation times varied widely and could not be clearly related to clinical severity.

AHG Deficiency.—Twenty-three patients, or 72% of the total, were found to have this type of hemophilia.

The results of coagulation tests performed on these are shown in Table 3. Again the serum prothrombin values of the "differential mixtures" are given in seconds in columns 3 through 8 and in per cent prothrombin consumption in columns 9 through 14. The patients are arranged in the table in three groups, as follows:

In Patients 10 through 18, diagnosis could be made either by the differential mixtures, by the thromboplastin generation test, or by both.

In Patients 19 through 26, diagnosis could not be established by the differential mixtures, either (a) because results were equivocal as discussed below or (b) because the patterns suggested the presence of an anticoagulant, i. e., failure of correction by any of the additives, as in Patients 24, 25, and 26.

In Patients 27 through 32, diagnosis rested on thromboplastin generation alone, since the effect of normal and abnormal additives was not determined.

Although grossly prolonged in the majority of patients, the coagulation time was normal in 6 of the 23 patients. It was only very slightly prolonged in three others. The serum prothrombin time was normal (>20 seconds) in two patients (27 and 31) and near normal in two others (23 and 30).

Again the difficulty of basing a diagnosis on the corrective ability of various plasma and sera is apparent. Results of such mixtures were clear-cut in nine patients (10 through 18) but were equivocal in five others (19 through 23). In the latter group either normal plasma or PTC deficient

TABLE 3.—*Summary of Coagulation Data in AHG Deficient Patients*

Patient	Coag. Time, Min.	Serum Prothrombin, Seconds						Prothrombin Consumption, %						Thromboplastin Generation			
		After Addition of*						After Addition of*						Plasma†		Serum†	
		Alone	N.P.	BaS	Ser.	AHG	PTC	Alone	N.P.	BaS	Ser.	AHG	PTC	Sec.	%	Sec.	%
10	>30	11.2	21.1	24.0	10.8	12.0	20.0	0	86	89	0	0	83	42.9	7	15.3	70
11	17	11.5	120.0	33.0	13.5	13.4	38.0	0	99	96	30	29	96	31.0	17	11.2	92
12	40	11.5	—	22.0	11.9	—	—	0	—	87	0	—	—	—	—	—	—
13	66	12.0	27.8	52.8	11.7	11.9	23.0	0	94	97	0	0	88	54.7	3	13.8	78
14	28	12.1	25.3	43.7	13.4	13.2	—	0	91	96	29	26	—	—	—	—	—
15	63	12.4	—	29.7	12.6	13.5	—	6	—	95	8	30	—	—	—	—	—
16	40	12.4	30.0	26.0	14.0	—	—	6	95	92	40	—	—	18.0	57	9.5	>100
17	69	12.6	18.8	28.8	13.4	12.2	24.3	8	80	95	29	0	90	22.9	36	11.8	88
18	77	14.3	22.8	25.0	13.9	11.2	21.4	48	88	90	39	0	86	40.0	8	10.0	100
19	>60	13.5	31.3	68.5	16.6	15.7	19.8	30	95	98	67	60	83	45.5	5	11.5	91
20	>75	14.1	18.2	27.6	16.0	15.0	18.4	46	78	94	68	55	79	46.0	5	7.0	>100
21	9	14.6	24.9	—	—	17.5	34.6	51	90	—	—	74	96	45.5	5	14.4	75
22	14	14.7	18.9	24.0	—	16.9	24.9	52	80	89	—	69	90	44.0	6	13.5	80
23	14	19.0	120.0	28.5	20.1	16.1	18.6	81	99	94	63	64	79	18.3	55	12.0	87
24	18	13.9	14.0	14.2	13.8	14.2	13.4	39	40	47	38	47	29	41.2	8	8.5	>100
25	9	14.2	14.5	—	15.0	14.8	15.1	47	50	—	55	53	57	24.8	28	9.5	>100
26	>120	13.3	14.4	14.4	13.4	13.3	14.5	28	48	48	29	28	50	40.0	8	15.0	73
27	14	20.6						85						30.2	18	9.4	>100
28	31	13.0						15						22.8	37	12.2	87
29	20	12.0						0						29.1	20	11.4	91
30	15	17.3						74						24.0	32	10.0	100
31	13	35.5						96						17.0	60	11.2	92
32	80	16.0						63						30.0	18	12.5	85

* Interpretation same as for Table 2.
† Interpretation same as for Table 2.

plasma failed to correct the clotting defect to the expected degree or else serum or AHG deficient plasma were more corrective than anticipated. The three patients exhibiting corrective patterns suggesting the presence of an inhibitor will be discussed further below. Thus in only 9 of the 17 patients could the corrective ability of various blood derivatives be considered typical of that expected in AHG deficiency.

In this type of hemophilia, as previously indicated for the PTC deficient group, results of the thromboplastin generation test were clear-cut, as noted in Table 3. The values recorded represent maximal thromboplastic activity for serum and plasma obtained from 2-5 minutes and from 3-10 minutes, respectively, after completion of the incubation mixture. All patients in this group exhibited normal activity when their serum was substituted into an otherwise normal system but showed varying degrees of diminution when their plasma was so substituted (Figure). The one possible exception (Patient 10, with but 70% thromboplastin generation obtained using his serum) was by all other criteria typical of AHG deficiency.

With three exceptions, the plasma prothrombin times of the patients ranged from 11 to 13.2 seconds (75% to 100%). In Patients 13 and 18, who are brothers, an inconstant and slight decrease in plasma prothrombin activity (55% to 69%) could be restored to 100% on the addition of 0.05 ml. of bovine Ac globulin (Bacto Ac Globulin, Difco Laboratories, Detroit) but remained unaffected on addition of serum. Prothrombin content was normal by the TAMe assay.* [9] While this finding suggests a diagnosis of Ac-globulin deficiency, the serum prothrombin data shown in Table 3 support a diagnosis of AHG deficiency. This evidence then suggests a combined deficiency in these brothers. The moderately prolonged plasma prothrombin time (14.6 seconds) of a third patient, Patient 21, could not be ascribed to a deficiency of Ac globulin or prothrombin and to date remains unexplained.

Bleeding times in excess of seven minutes were recorded in 8 of the 19 AHG deficient patients so studied.

In this group of 23 AHG deficient patients, as previously noted for the PTC deficient patients, results of tests were, in general, "less abnormal" in those whose hemorrhagic manifestations were considered mild to moderate in severity and "more abnormal" in those with markedly severe disease. Thus of the six with normal coagulation times, five were felt to have mild to moderately active disease; in four of these serum prothrombin times were either normal or nearly so, and in four thromboplastin generation exceeded 28%. Of those with moderate to marked disease activity, only one exhibited a normal coagulation time, none exceeded 52% prothrombin consumption, and in only one did thromboplastin generation exceed 17%.

Circulating Anticoagulants.—The failure of the various blood derivatives to correct the serum prothrombin times of Patients 24 through 26 suggested the presence of an inhibitor or anticoagulant. Two of these three were repeatedly tested and for interest are here considered in some detail.

Patient 26.—This patient, a boy of 14 years, was typical of reported hemophiliacs whose course has become complicated by an anticoagulant. Hemorrhagic bouts were frequent, severe, and crippling; treatment over the years consisted of multiple infusions of whole blood, plasma, and Cohn's Fraction I. Recently the boy has shown insignificant response even to infusions of large quantities of plasma, exchange transfusion, as well as prolonged steroid therapy, and both clinical and laboratory evidence of an anticoagulant has persisted for three years.

Patient 24.—By contrast, this patient was first tested at the age of 2 months, when an abnormal serum prothrombin time was completely corrected by normal plasma and normal $BaSO_4$ plasma but not by serum. At the age of 11 months, similar tests yielded entirely different results, suggesting the presence of an anticoagulant, as shown in Table 3. During the interval separating the laboratory tests, hemorrhagic bouts were minor and no infusions of whole blood, plasma, or derivatives

* Dr. Helen Glueck performed this assay.

TABLE 4.—*Inhibitory Effect of Serum from Different Sources on Initial Stage of Thromboplastin Generation*

Source of Serum	A Minutes		B Minutes
	3	9	3
Normal subject	88	73	83
Uncomplicated hemophilia, Patient 16	76	52	91
Hemophilia complicated by anticoagulant, Patient 24	58	42	100
Patient 26	57	17	90

For each subject two mixtures (A & B) were prepared containing 0.2 ml. each of normal barium sulfate plasma, calcium chloride, and normal serum. These were both incubated 10 minutes at 37 C; to "A" 0.1 ml. of subject's serum was added prior to incubation, and to "B" 0.1 ml. of the same serum was added immediately after the incubation period. Both systems were then completed by the addition of 0.2 ml. of platelets and thromboplastin generation measured at the intervals indicated. Results expressed in per cent.

had been given. In vitro evidence of the anticoagulant, still present at 14 months, spontaneously disappeared at age 17 months. The coagulation time, determined repeatedly, never exceeded 19 minutes.

In an attempt to elucidate the site of action of the inhibitors and for purposes of comparing these patients, two types of procedures were carried out:

1. To determine whether the anticoagulant interfered with the interaction of factors contributed by $BaSO_4$ plasma and serum, a modification of the technique suggested by Hougie[10] was used. This technique is based on the finding that pre-incubation of antihemophilic globulin, serum, and calcium leads to a more rapid formation of thromboplastin when labile factor and platelets are subsequently added than when no such pre-incubation period is permitted.[11] Hougie demonstrated that the anticoagulants of three patients inhibited the generation of thromboplastin by preventing this reaction between antihemophilic globulin and serum. Results are shown in Table 4. The reduction in thromboplastin generation at the three-minute interval in Patients 24 and 26 suggests a similarity of action, i. e., interference between the interaction of factors contributed by normal plasma and serum, though not to the same degree as shown by the patients of Hougie. The further reduction in all three patients (16, 24, 26) at the nine-minute interval suggests, in addition, the presence of an inhibitor with antithromboplastin activity, being greater in degree in Patient 26 than in the others.

2. To determine whether the anticoagulant inactivated solely the factor contributed by normal $BaSO_4$ plasma, the procedure outlined under Table 5 was devised. The results indicate clearly a difference in the anticoagulant activity of the plasma and serum of Patient 26 as compared with that of Patient 24. With the passage of time, both blood derivatives of Patient 26 appear to inactivate that factor contributed by normal $BaSO_4$ plasma (presumably the antihemophilic globulin) necessary for the generation of thromboplastin, whereas neither derivative of Patient 24 or of the normal control do so. Both patients' blood derivatives had been stored in the frozen state for approximately 30 days prior to the above tests. It therefore remains possible that the inhibitor of Patient 24 was unstable to such storage.

Comment

The clinical features of "the hemophilias" have not been stressed in the present report, since, as previously stated, it was felt that little could be added to an already existent and voluminous literature. Rather, attention has been focused on the laboratory diagnosis of these disorders, employing methods in common usage.

Our results confirm those of others[12-14] in emphasizing the value of the thromboplastin generation test in the differential diagnosis of these disorders. Relying largely on this test, we clearly separated the 32 patients into two groups: 9, or approximately 28%, having an isolated serum defect and therefore identified as PTC deficiency, and 23, or approximately 72%, having an isolated plasma defect and therefore identified as AHG deficiency. The inci-

TABLE 5.—*Inhibition of the Antihemophilic Factor by the Plasma and Serum from Different Sources as Measured by the Thromboplastin Generation Test*

Source of Blood Derivative	Plasma		Serum	
	Without Incubation	After Incubation	Without Incubation	After Incubation
Normal	100	100	100	100
Patient 24	100	100	100	100
Patient 26	80	23	100	8

Equal parts of patient plasma (or serum) and normal $BaSO_4$ plasma were mixed. Either immediately or after incubation of this mixture at room temperature for 60 minutes, the appropriate dilution was made and the system completed with normal platelets, normal serum, and $CaCl_2$. Thromboplastin generation was determined after four minutes. Results expressed in per cent.

dence of PTC deficiency is thus somewhat higher than in other reported series.[15-17] The lack of PTA [18] and PTF-D [19] patients is taken as evidence of the relative rarity of these disorders.

By comparison with the thromboplastin generation test, the "differential mixture" test often gave results that were either difficult to interpret or, in fact, strongly suggestive of an alternative but incorrect diagnosis. There are several possible explanations for these shortcomings. In the first place, as might be expected, results are usually reliable and interpretation easy when the patient's initial prothrombin consumption is quite poor. However, this is often not the case when the patient's initial prothrombin consumption approaches the normal range. Secondly, since it appears [20] that only a small percentage of the normal quantity of AHG or PTC factors is required for prothrombin consumption to be normal, it is obvious that in performing such differential tests, one should employ only pathologic plasma from patients with severe AHG or PTC deficiency. Unfortunately this was not always done in the present study and may account for some of the difficulties encountered. Stefanini [21] has reported similar experiences. Finally, the type of $BaSO_4$ solution used has a bearing on the outcome of such differential tests. As previously mentioned, the prothrombin consumption of some of the PTC deficient patients was aided to a greater extent than expected by the addition of normal $BaSO_4$ plasma. Since a solution containing 50 mg. $BaSO_4$ per cubic centimeter of plasma is necessary for complete removal of the PTC factor, and since plasma adsorbed by a solution containing but 30 mg. $BaSO_4$ may be expected to enhance the prothrombin consumption of a PTC patient by about 30%,[22] the use of a solution containing 35 mg. $BaSO_4$ per milliliter of plasma (as employed throughout in this study) might be expected to leave behind some PTC factor which then complements that amount present in the patient's blood and enhances the utilization of prothrombin.

Normal coagulation times as well as normal utilization of prothrombin are no longer unexpected findings in some patients with "hemophilia."[1] It was, however, surprising that as many as 9 patients with normal coagulation times occurred in this group of 32 (3 of 9 PTC patients and 6 of 23 AHG patients). Serum prothrombin times were normal in three patients (one with PTC and two with AHG deficiency).

The degree of reduction in the antihemophilic globulin has been correlated not only with the outcome of various coagulation tests, as mentioned above, but also with severity of hemorrhagic manifestations.[23] In the present study there was no close correlation between results of the diagnostic tests used and clinical severity for the group as a whole. In certain persons, however, relatively mild disease was present when coagulation times and prothrombin consumption were normal and thromboplastin generation relatively high. However, in addition to those with an apparent correlation there were several exceptions. These may stem not only from the fact that the tests herein used are not quantitative but also from the difficulty of classifying the clinical severity of these disorders. It is equally true that the incidence of hemorrhagic manifestations does not always depend solely on the degree of deficiency of one of the plasma factors.[1]

Prolonged bleeding times have been noted before in "hemophilia," but again it was somewhat surprising that this finding occurred in almost one-half of the AHG deficient and one-fourth of the PTC deficient patients in this study. However, a diagnosis of "vascular hemophilia"[24,25] or combined vascular and humoral defect seemed justified in only one of these patients, a 4½-year-old child in whom the bleeding time was 7½ minutes and the thromboplastin generation but 60% (using his plasma in an otherwise normal system). Coagulation time and serum prothrombin were normal. His mother, whose history suggested "pseudohemophilia," exhibited a prolonged bleeding time but normal thromboplastin

generation. The latter test was typical of AHG deficiency in her brother. Capillary loops of the nailbed in each of these three, as well as in several other patients whose bleeding times were prolonged, were not considered abnormal. It may well be that the finding of prolonged bleeding times in a number of these patients is due simply to the fact that larger vessels were injured in them. Certainly the technique is difficult to standardize and this possibility remains open. Observations made of Patient 3 might be used to support this contention but might also be interpreted as indicating that small-vessel bleeding is to some extent controlled by the integrity of humoral factors. In this child plasma infusions not only restored the prolonged coagulation time and serum prothrombin time to normal but also completely corrected a bleeding time of 60 minutes as well. Schulman has recorded similar results.[24]

Additional findings of interest were the prolonged plasma prothrombin times in three patients with AHG deficiency. Similar observations have been made by others.[1] While the explanation in one of the patients remains obscure, the results of tests in the other two suggest a combined deficiency of Ac globulin and the antihemophilic factor. Whether the former deficiency is transient, as has been reported in a variety of disease states,[26] or permanent has not been established as yet but has been found in these brothers in symptom-free intervals as well as during hemorrhagic bouts.

The presence of anticoagulant activity in 3 of the 23 patients with AHG deficiency makes the incidence in this series comparable to that noted by Frommeyer[27] in a similar group of hemophilic adults in this country, but it is much higher than that noted in England.[10] Studying both hemophiliac patients who had received many transfusions and nonhemophiliac patients who had never received such therapy, Hougie[10] has suggested that all such anticoagulants are probably identical in nature and action, being antithromboplastinogens but not antithromboplastins. Though studies in our patients are admittedly incomplete, the results certainly suggest a lack of identity not only in site of action but also in origin and duration as well.

Summary

A group of 32 "hemophiliac" children has been studied and classified according to the specific coagulation defect. There were 9 patients (28%) with plasma thromboplastin component (PTC) deficiency and 23 patients (72%) with antihemophilic globulin (AHG) deficiency.

As a diagnostic tool the thromboplastin generation test was found to be superior to the prothrombin consumption of mixtures of various blood derivatives with patients' blood and could be relied upon even in those whose clotting time and serum prothrombin time were normal.

In three patients a prolonged plasma prothrombin time was observed, and in two of these evidence for a concomitant deficiency of Ac globulin and AHG has been presented. Three other AHG patients demonstrated circulating anticoagulants, two of whom were studied further in an attempt to elucidate the site of anticoagulant action.

A prolonged bleeding time was recorded in several patients, and its significance is discussed.

The Children's Hospital Research Foundation, Elland Avenue and Bethesda (Dr. Lahey).

REFERENCES

1. Stefanini, M., and Dameshek, W.: The Hemorrhagic Disorders, New York, Grune & Stratton, Inc., 1955.

2. Lee, R. I., and White, P. D.: A Clinical Study of the Coagulation Time of Blood, Am. J. Med. Sc. 145:495-503, 1913.

3. Duke, W. W.: The Relation of Blood Platelets to Hemorrhagic Disease: Description of a Method for Determining the Bleeding Time and Coagulation Time and Report of 3 Cases of Hemorrhagic Disease Relieved by Transfusion, J. A. M. A. 55:1185-1192, 1910.

4. Dameshek, W.: A Method for the Simultaneous Enumeration of Blood Platelets and Reticulocytes, with Consideration of Normal Blood Platelet Count in Men and in Women, Arch. Int. Med. 50:579-589, 1932.

5. Quick, A. J.: The Clinical Application of the Hippuric Acid and the Prothrombin Tests, Am. J. Clin. Path. 10:222-233, 1940.

6. Stefanini, M., and Crosby, W. H.: The One-Stage Prothrombin Consumption Test: Clinical Value in the Identification of the Thromboplastin-Deficiency Diseases, Blood 5:964-972, 1950.

7. Biggs, R., and Douglas, A. S.: Thromboplastin Generation Test, J. Clin. Path. 6:23-29, 1953.

8. Ramot, B.; Angelopoulos, B., and Singer, K.: Plasma Thromboplastin Antecedent Deficiency, A. M. A. Arch. Int. Med. 95:705-712, 1955.

9. Glueck, H. I.; Sherry, S., and Troll, W.: Assay of Plasma Prothrombin with a Synthetic Substrate, Proc. Soc. Exper. Biol. & Med. 87: 646-650, 1954.

10. Hougie, C., and Fearnley, M. E.: The Nature and Action of Circulating Anticoagulants, Acta haemat. 12:1-10, 1954.

11. Biggs, R.; Douglas, A. S., and Macfarlane, R. G.: The Initial Stages of Blood coagulation, J. Physiol. 122:538-553, 1953.

12. Bergsagel, D. E.; Setna, S. S.; Cartwright, G. E., and Wintrobe, M. M.: Mild PTC (Plasma Thromboplastin Component) Deficiency Occurring in 2 Brothers, Blood 9:866-874, 1954.

13. Macfarlane, R. G.: Symposium: What is Hemophilia? Hemophilia, Christmas Disease, and Matters of Terminology, Blood 9:258-264, 1954.

14. Ramot, B.; Angelopoulos, B., and Singer, K.: Variable Manifestations of Plasma Thromboplastin Component Deficiency, J. Lab. & Clin. Med. 46:80-88, 1955.

15. Rosenthal, R. L.: Hemophilia and Hemophilia-like Diseases Caused by Deficiencies in Plasma Thromboplastin Factors: Anti-Hemophilic Globulin (AHG), Plasma Thromboplastin Component (PTC) and Plasma Thromboplastin Antecedent (PTA), Am. J. Med. 17:57-69, 1954.

16. Soulier, J. P., and Larrieu, M. J.: Differentiation of Hemophilia into 2 Groups: A Study of 33 Cases, New England J. Med. 249:547-553, 1953.

17. Frick, P. G.: The Relative Incidence of Anti-Hemophilic Globulin (AHG), Plasma Thromboplastin Component (PTC), and Plasma Thromboplastin Antecedent (PTA) Deficiency: A Study of 55 Cases, J. Lab. & Clin. Med. 43:860-866, 1954.

18. Rosenthal, R. L.; Dreskin, O. H., and Rosenthal, N.: New Hemophilia-like Disease Caused by a Deficiency of a Third Plasma Thromboplastin Factor, Proc. Soc. Exper. Biol. & Med. 82:171-174, 1953.

19. Spaet, T. H.; Aggeler, P. M., and Kinsell, B. G.: A Possible Fourth Plasma Thromboplastin Component, J. Clin. Invest. 33:1095-1102, 1954.

20. Macfarlane, R. G., and Biggs, R.: Thromboplastin Generation with Particular Reference to Hæmophilia, Sang 26:181-190, 1955.

21. Stefanini, M.: Symposium: What is Hemophilia? Hemophilia: Specific Entity or Syndrome? Blood 9:273-280, 1954.

22. White, S. G.; Aggeler, P. M., and Glendening, M. B.: Plasma Thromboplastin Component (PTC): A Hitherto Unrecognized Blood Coagulation Factor: Case Report of PTC Deficiency, Blood 8:101-124, 1953.

23. Brinkhous, K. M., and Graham, J. B.: Symposium: What is Hemophilia? Hemophilia and the Hemophiloid States, Blood 9:254-257, 1954.

24. Schulman, I.; Smith, C. H.; Erlandson, M., and Fort, E.: Vascular Hemophilia: A Familial Hemorrhagic Disease in Males and Females Characterized by Combined Antihemophilic Globulin Deficiency and Vascular Abnormality, Society Transactions, A. M. A. Am. J. Dis. Child. 90:526-527, 1955.

25. Darte, J. M. M.: Defect of Antihemophilic Globulin in von Willebrand's Disease, Society Transactions, A. M. A. Am. J. Dis. Child. 90:561-562, 1955.

26. Stefanini, M.: Activity of Plasma Labile Factor in Disease, Lancet, 1:606-610, 1951.

27. Frommeyer, W. B. Jr.; Epstein, R. D., and Taylor, F. H. L.: Refractoriness in Hemophilia to Coagulation-Promoting Agents: Whole Blood and Plasma Derivatives, Blood 5:401-420, 1950.

Vitamin-D-Resistant Rickets

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The familial character of vitamin-D-resistant rickets has been mentioned in the past, yet the exact mode of its inheritance has been neglected. There have been postulations of the dominant character of the trait, but this has been surmised from a few isolated cases which have not received sufficient attention with regard to the entire family history.

The disease was first described by Albright, Butler, and Bloomberg [1] and the familial tendency was soon recognized by Gill[2] and Christensen.[3] Since Pederson and McCarroll[4] found this disease to be a leading cause of dwarfism in their clinic, the determination of the mechanism of inheritance is important from the standpoint of family counseling.

The purpose of this paper is to report an additional case of vitamin-D-resistant rickets in a child whose family history is rather striking in that five generations of her family show members to be affected with this deforming condition. An attempt is made to draw some conclusions from the information regarding the case presented. It is hoped that others may present complete surveys when possible in order to more definitely establish the mode of transmission.

Report of a Case

An 11-year-old white girl (Fig. 1, *center*) was referred to the University of Virginia Hospital because of abnormal blood chemical findings associated with a clinical picture of rickets.

Bowing of the legs had first become apparent at the age of 13 or 14 months, when the child first began to walk. By the time that she was 2 years old the bowing was distinct and has since progressed.

The patient had received routine cod liver oil from time to time during the first seven or eight years of life with no appreciable effect on the rickets. During the several years preceding admittance to the hospital the patient had received no therapy other than a two-months course of vitamins A and D in unknown dosage just prior to admission.

The past medical history was unrelated to her illness. In the past she had received a balanced diet. Socially she was well adjusted and was doing well in the fifth grade in school.

The physical examination showed the patient to be an alert, well-nourished, 11-year-old white girl of short stature with marked bowing of the legs and widening of the distal ends of the ulnae and radii bilaterally. The temperature, pulse, respirations, and blood pressure were normal. The weight was 29.5 kg. and the height 125 cm., which is below the third percentile for the patient's age. The upper-lower ratio was 1.05 (expected value 1.01-1.00). Axillary hair was sparse, and the breasts showed early pubescent changes. The liver was palpable 3 cm. below the right costal margin and was smooth and nontender. The remaining physical examination, including a slit-lamp examination of the eyes, was not remarkable.

The routine urine examination showed an acid reaction, a specific gravity of 1.022, a negative Sulkowitch test on several occasions, a normal microscopic examination, and no albumin or reducing substances. The white blood cell count, differential white blood cell count, hemoglobin, and hematocrit were normal. The blood urea was 19.7 mg. per 100 cc.; the plasma chloride, 108 mEq. per liter; the plasma carbon dioxide combining power, 25.2 mEq. per liter; the serum sodium, 140 mEq. per liter; the serum potassium, 4.3 mEq. per liter, and the serum magnesium 2.0 mEq. per liter. The sulfobromophthalein sodium (Bromsulfalein) test showed 3.5% retention in one hour. The cephalin-cholesterol flocculation was 2+, the thymol turbidity 7.8 thymol turbidity units, the later value being in the upper range of normal, and the total protein 7.2 gm. per 100 cc. with a normal albumin-globulin ratio. Laboratory results referable to calcium metabolism are listed in Table 1.

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TABLE 1.—*Laboratory Results Referable to Calcium Metabolism*

Date	Blood			Urine			Comment
	Calcium, Mg/100 Cc.	Phosphorus, Mg/100 Cc.	Alkaline Phosphatase, Bodansky Units	Volume, Cc.	Calcium, Mg/100 Cc.	Phosphorus Mg/100 Cc.	
9/28/54	11.8	1.9	19.2				
11/ 5/54	14.1	2.5	24.7				
11/ 8/54	11.5	2.8		1650	24.6	501	
11/13/54	10.3	3.3					
11/14/54				450	22.0	133	
11/16/54							Vitamin D begun
1/ 5/55	10.5	3.3	12.1				X-ray healing
5/21/56	9.6	3.4	15.2				X-ray healing

An intravenous pyelogram showed excellent excretion of dye in 10 minutes, and a normal collecting system was outlined. Other x-rays showed a generalized decalcification of all the long bones, widening of the epiphyseal lines, and cupping of the metaphyses. X-rays of the chest were normal.

Inasmuch as routine doses of multivitamins had been ineffective in controlling the advance of deformities and because a diagnosis of vitamin-D-resistant rickets had been made, the patient was started on 300,000 units of vitamin D daily, with routine Sulkowitch tests being performed on the urine. After a month and a half of therapy the x-rays of the long bones showed early healing of the rachitic process but the chemical determinations showed only a decrease in the alkaline phosphatase and slight increase in serum phosphorus levels. She was subsequently followed in another clinic until seen at a University Hospital clinic visit 18 months following the institution of therapy. She had continued to take her medication as prescribed until six months prior to her last visit, when the dose was reduced elsewhere to 100,000 units of vitamin D daily. X-ray examination showed further healing, but blood chemical studies were essentially unchanged.

Comment

In such a patient it is necessary that other diseases be ruled out. In this case rachitic rickets could be dismissed, since by history the patient had not responded to the usual dose of vitamin D over a period of several years. Hypophosphatasia was not responsible for the rickets, since the patient had responded to massive doses of vitamin D, alkaline phosphatase was elevated, and the serum phosphorus depressed. Renal rickets did not appear to be present, since there was no chloride acidosis and the usual tests for renal function and electrolyte studies were within normal limits. Finally, it would appear that cystinosis would be ruled out by the absence of glycosuria, normal renal-function studies, and absence of cystine crystals in the urine and cornea. Paper chromatographic studies were not done. The changes in bone as demonstrated by x-ray examination substantiated the diagnosis of vitamin-D-resistant rickets.

Because of the clinical course of the patient and the blood chemical studies (Table 1) following the institution of vitamin-D therapy, one might wonder at the values obtained. In the presence of x-ray evidence of healing, the return of a positive Sulkowitch test, and the depression of the alkaline phosphatase, one would ordinarily expect an increase in the serum phosphorus. There was a minor increase in the serum phosphorus but not to the degree expected. We have no adequate explanation for these findings, but it should be noted that a similar response to therapy has been previously mentioned.[5]

In the adult patients examined (Table 2) it is noted that the alkaline phosphatase values are normal, the serum calcium values are low or normal, and the serum phosphorus values are depressed. These findings would support the contention of Albright [6] that following puberty the disease becomes a chemical osteomalacia. The findings of severe degree of deformity in some adults and moderate deformities in other members of the family supports the opinion of Pederson and McCarroll that severly affected adults probably need treatment.

In the light of present knowledge, one can find cases with a variety of names in the medical literature which were undoubtedly unrecognized vitamin-D-resistant rick-

TABLE 2.—*Blood Chemical Values on Relatives*

Patient	Age, Yr.	Calcium, Mg/100 Cc.	Phosphorus, Mg/100 Cc.	Alkaline Phosphatase, Bodansky Units	Clinically Diseased	Degree of Disease
AI,2	35+	11.0	2.1	3.4	yes	moderate
AI,1	36	10.6	2.5	2.6	yes	severe
Pr. 8†	25	8.2	1.7	3.2	yes	severe
Pr. 11†	17	7.7	2.5	*	yes	severe
Pr. 4	4	10.6	2.3	17.6	yes	moderate
DI,2†	2	8.5	3.2	18.6	no	
DI,3†	4	9.9	6.7	6.0	no	
Pr. 1	3	9.3	5.4	4.3	no	
DI,1	6/12	9.0	5.6	10.1	no	
Pr. 2	11/12	8.4	5.1	5.5	no	

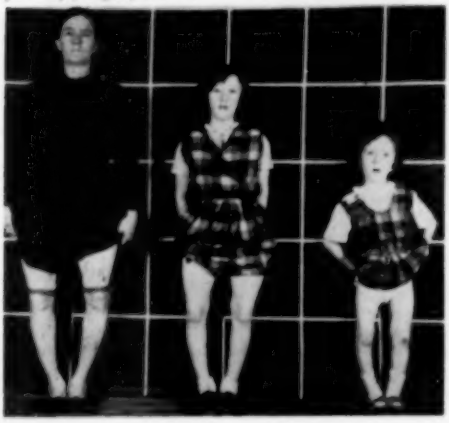
* Blood too hemolyzed to be of value in this test.
† Blood in these patients considerably hemolyzed.

ets. Several of these older cases are interesting because of the rather strong suggestion of the familial character. Baagøe [7] in 1924 reported a case in which five siblings, the mother, and maternal aunt and uncle were affected. Several other reports showed the disease occurring in more than one sibling where one of the parents was affected.[8,9] More recently Christensen [3] reported a case of a patient both of whose parents were affected, but no detailed account of the family tree was included in the report. In 1949 McCune [10] reported the occurrence of the condition in identical twins.

The report of Pederson and McCarroll [4] bears genetic significance. These authors reported 25 affected children, of which 16 fell into 10 family groups in which one parent was similarly affected. The history revealed the presence of the condition in more distant relatives in several families. Of the more seriously affected families presented by these authors, one involved three generations with nine persons affected and a second case showed five persons affected in four generations but in their cases no mention is made of the number of unaffected persons in these families.

In order to say that all of the rachitic members of this family are suffering from the same illness, it has been necessary to extrapolate from the information obtained from our patient, from that of another member of the family adequately studied in another institution, and from less definitive information of other members spread over three States. The pitfalls of such measures are well recognized. In addition, the statistical limitations resulting from the small number of persons involved make definite conclusions difficult. However, certain postulations can be made on the basis of the accompanying pedigree.

Fig. 1.—*Left*, AI, 2; *center*, Pr. 9 (patient reported); *right*, Pr. 4.



The family tree is depicted in Figure 3. It should be noted that of the 10 persons represented by gray the authors possess photographs of three of the living ones (AI; 5,6,7) showing moderate to severe rachitic deformities, but no laboratory work was available. Two others (Pr. and DI) were examined by other physicians but again no laboratory work was obtained. Two were sisters (AI; 3,4) of the informant and were dead, and the remaining three of these persons were the mother (AII, 1), aunt (AII, 2), and grandfather (AIII, 1) of the informant, all of whom were clearly remembered as being deformed.

Fig. 2A.—AI, 1.

Fig. 2B.—AI, 5.

Fig. 2C.—AI, 6.

Fig. 2D.—AI, 7.

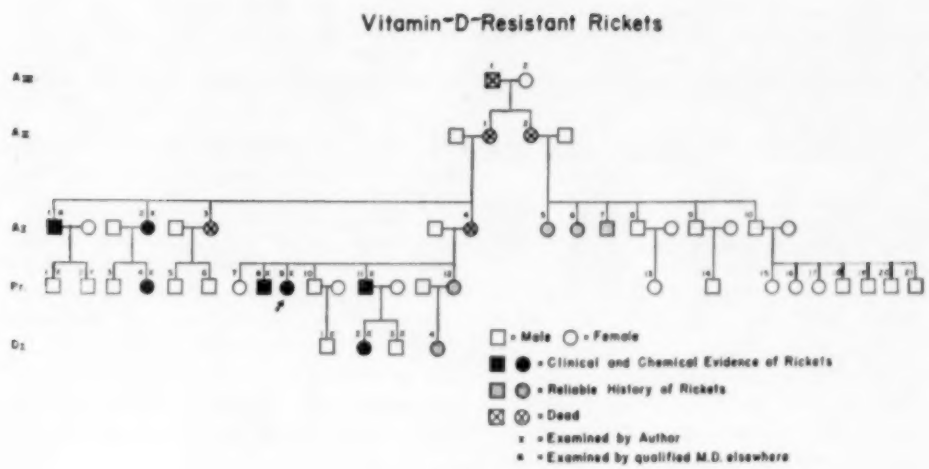

Vitamin-D-Resistant Rickets
A III
A II
A I
Pr
D I
□ = Male ○ = Female
■ ● = Clinical and Chemical Evidence of Rickets
▣ ◎ = Reliable History of Rickets
⊠ ⊗ = Dead
x = Examined by Author
* = Examined by qualified M.D. elsewhere

Figure 3

Of the seven members of the family depicted in black, pictures of four (Pr; Pr. 4; AI, 1; AI, 2) were available. AI, 1 is severely affected and has undergone 18 orthopedic operations elsewhere, whereas the other three are only moderately affected. The other persons depicted in black are so shown because of history and blood chemical determinations. One of the latter (DI, 2) was found to have changes compatible with the diagnosis of rachitic rickets or vitamin-D-resistant rickets, but the infant was too young to manifest clinical evidence of the condition. The child had received no supplemental vitamins but had been given an adequate and balanced diet.

Of the 37 related persons of this family, 20 are males and 17 are females. Of the affected members, 5 are males and 12 are females. The ratio of affected females to males is approximately two to one, but the deviation is not statistically significant. In every generation, excepting the fifth, there are members of both sexes affected. If it is considered that the condition is the result of the action of a dominant gene and affected and unaffected siblings are counted in sibships where one parent is affected (discounting deaths in these sibships), it is found that 14 are affected and 11 are unaffected. The χ-square value is 0.2, which corresponds to a probability level between 50% and 70%. This is a value of high statistical importance.

The findings in this family strongly support the contention that vitamin-D-resistant rickets is due to a dominant mode of inheritance. It is impossible to assess the degree of penetrance of this gene, but the fact that members of the family are affected to varying degrees is evidence of the variability of its expression.

Summary

A case of vitamin-D-resistant rickets is presented. It is postulated, on the basis of a pedigree involving five generations, that this disease is the result of a single dominant autosomal gene of variable expressiveness.

Dr. William Happer and the staff of the Caldwell County, North Carolina Health Department, aided in securing much of the information used in this family study.

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REFERENCES

1. Albright, F.; Butler, A. M., and Bloomberg, E.: Rickets Resistant to Vitamin D Therapy, Am. J. Dis. Child. 54:529 (Sept.) 1937.

2. Gill, M. A.: Vitamin-Resistant Rickets, Arch. Dis. Childhood 14:50 (March) 1939.

3. Christensen, J. F.: Three Familial Cases of Atypical Late Rickets, Acta Pædiat. 28:247, 1941.

4. Pederson, H. E., and McCarroll, H. R.: Vitamin-Resistant Rickets, J. Bone & Joint Surg. 33-A: 203 (Jan.) 1951.

5. Nelson, W. E.: Textbook of Pediatrics, Ed. 6, Philadelphia, W. B. Saunders Company, 1954, p. 1325.

6. Albright, F., and Reifenstein, E. C.: Parathyroid Glands and Metabolic Bone Disease: Selected Studies, Baltimore, Williams & Wilkins Company, 1948, p. 218.

7. Baagoe, K.: Tardy Rickets, Ugesk. Læger 86:175 (Feb. 28) 1924; cited by Christensen, J. F.

8. Jampolis, M., and Londe, S.: The Need for Larger Doses of Viosterol in Severe Rickets (Osteomalacia Type), J. A. M. A. 98:1637 (May 7) 1932.

9. Lightwood, R., and Wood, I. J.: Familial Rickets of Obscure Etiology, Proc. Roy. Soc. Med. 26:277 (Jan.) 1933.

10. McCune, D. J.: Refractory Rickets in Identical Twins: Society Transactions, Am. J. Dis. Child. 63:1008 (May) 1942.

Thyroidal Accumulation of Radioiodine in Children

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Although a large volume of information on the radioiodine uptake by the thyroid of the adult is available, there is relatively little such information concerning the infant and child. For the most part, published data for the child or infant relate to the normal or hypothyroid person and pertain to the period between 24 and 96 hours following the administration of the radioiodine test dose.

The present study concerns the thyroid uptake of radioiodine as a function of the status of the thyroid gland, the age of the patient, and the time after the administration of the test dose. It provides data on the effect of the thyroid-stimulating hormone (TSH) on thyroidal accumulation of radioiodine in the euthyroid, the primary hypothyroid, and the pituitary hypothyroid child.

In a recent paper by Martmer, Corrigan, Charbeneau, and Sosin,[1] the 24-hour radioiodine uptake in 65 premature infants was reported as being within the limits of normal for children and adults. Middlesworth[2] found that the 24-hour uptake of radioiodine in the 1- to 3-day-old normal full-term infant ranged between 46% and 97% of the administered dose. In the adult such high levels would be indicative of hyperthyroidism. Quimby and McCune[3] studied the thyroid uptake of radioiodine at 48 hours in 54 children under the age of 15 years. Thirty-three were euthyroid and showed an average 48-hour uptake of 12.0%, with a range from 4% to 20%; there was no discernible relationship between uptake and age of the child. Five children who were clearly hypothyroid showed uptakes of less than 1%, and two children who were clearly thyrotoxic had uptakes of 34% and 60%, respectively. Reilly and Bayer,[4] in a study of thyroid uptake and urinary excretion of I^{131} in 25 euthyroid children and in 5 congenitally hypothyroid children, found the maximum uptake to occur between 24 and 48 hours and showed that the normal thyroid took up from 8% to 30% of the administered dose, while the uptake in the thyroid of the cretinous children was between 1% and 2%.

Methods and Materials

The present series includes all patients under the age of 18 years studied in the Radioiodine Laboratory at the University of California School of Medicine for whom adequate records were available.* Thirty-four euthyroid, sixteen primary hypothyroid, sixteen pituitary or secondary hypothyroid, and seventeen hyperthyroid children were studied. In each case the clinical record was carefully reviewed. The final diagnosis was based on the clinical evaluation, the serum protein-bound iodine level, the bone age, and, in some cases, on the clinical response to thyroid therapy. The radioiodine uptake and the response to thyrotropic hormone were not used in arriving at the diagnosis. The euthyroid group was composed chiefly of children who were of small stature but had no other abnormality, were mentally retarded, or had Legg-Perthes' disease; all appeared to have normal thyroid function. The primary hypothyroid group included those with evidence of hypothyroidism but with no clinical or laboratory evidence of other endocrine disorder; none had a demonstrable goiter. The pituitary or secondary hypothyroid group included those nongoitrous children who ex-

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* Seven children with sporadic goitrous hypothyroidism are being reported elsewhere. The thyroids in these children exhibited bizarre uptake curves suggesting that there was in each case a specific inborn error of metabolism in the thyroid; it was thought best to consider them as a separate group.

TABLE 1.—*Thyroid Uptake of I^{131} Following Oral Administration (Average Values and Range of Values)*

Thyroid Status	Time After Administration					
	3 Hours		5 Hours		24 Hours	
	Average, %	Range, %	Average, %	Range, %	Average, %	Range, %
Euthyroid	13.1	6-28	15.7	8-29	22.1	12-45
Primary hypothyroid	7.7	0-20	7.0	1-13	4.9	2-12
Secondary hypothyroid	10.9	3-17	12.0	6-22	19.4	9-37
Hyperthyroid	55.0	23-85	63.0	42-78	66.0	48-79

hibited evidence of hypothyroidism together with other stigmata of pituitary dysfunction (sexual infantilism, low gonadotropins, low urinary 17-ketosteroids, short stature but normal body proportions, or radiological evidence of erosion of the sella). Among the patients in this group were one with a craniopharyngioma and two with brain tumors which caused enlargement of the pituitary fossa and erosion of the sella. The hyperthyroid children exhibited the usual signs and symptoms of hyperthyroidism and ultimately were shown to improve on antithyroid therapy.

The radioiodine isotope with a half-life of eight days (I^{131}) was used in all cases. The radioiodine was carrier-free and was administered either orally by paper cup or through a polyethylene stomach tube. A scintillation counter was used to measure the radioiodine uptake. The neck count was corrected for general body background by subtracting the count obtained over the thigh. The thyroid uptake was calculated as per cent of the administered dose. Details of the counting technique have been presented previously.[5]

Patients who were to be given thyroid-stimulating hormone first received a 24-hour radioiodine uptake study. Five- to fifteen-milligram doses of TSH were then administered intramuscularly at intervals of 12 hours for a total of four doses,[6] and the uptake study was repeated.

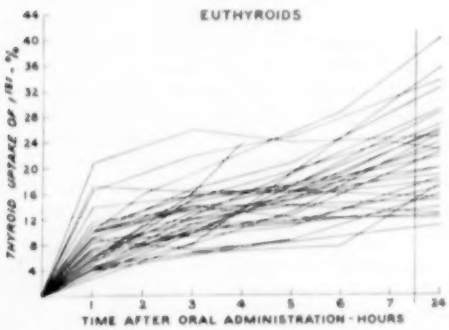

Fig. 1.—Thyroid uptake of radioiodine in 34 euthyroid children between 12 days and 17 years of age.

Results and Comment

Euthyroid Group.—The thyroid radioiodine uptake curves for 1 to 24 hours are presented in Figure 1. The average values and ranges of values are shown in Table 1. At three hours, the average thyroidal uptake was 13.1% of the administered dose, while, at five hours, the average was 15.7%. At 24 hours the average was 22.1%; the range was from 12% to 45%, with only one value above 36%. The youngest patient was 12 days of age and the oldest 17 years of age. Scatter diagrams in which the per cent uptake was plotted against age for 1-, 3-, 5-, and 24-hour uptakes failed to show any discernible relationship between age and uptake.

The effect of thyrotropic hormone on the 24-hour uptake in 20 euthyroid patients is shown in Figure 2 and Table 2. The average uptake before TSH was 22.1%, whereas the average after TSH was 33.1%. The maximum increase in this group was 22%; the average increase was 11%. In several patients TSH had no effect on the uptake, and in two patients there was an apparent decrease of 1% and 2%, respectively; however, variations of ± 1% to 3% are within the limits of the measurements.

Primary, Nongoitrous, Hypothyroid Group.—In terms of per cent of the administered dose, the thyroid uptake at three hours ranged from 0 to 20, with an average of 7.7 (Fig. 3 and Table 1). At five hours the range was from 1% to 13%, and the average was 7.0%. At 24 hours the range was from 2% to 12%, with an average of 4.9%.

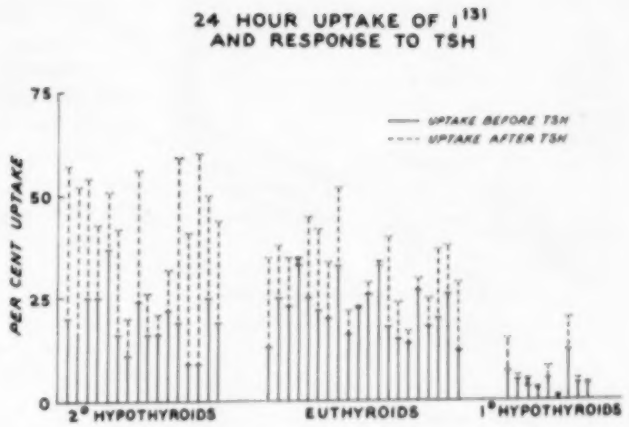

Fig. 2.—Effect of thyrotropic hormone on the 24-hour uptake of radioiodine in euthyroid, primary hypothyroid, and secondary hypothyroid children.

TABLE 2.—*Effect of TSH on Thyroid Uptake of I^{131} Twenty-Four Hours After Oral Administration*

Thyroid Status	Average Uptake Before T8H	Uptake After T8H		
		Average	Average Increase	Maximum Increase
Euthyroid	22.1	33.1	11	22
Primary hypothyroid	4.9	7.1	2.2	8
Secondary hypothyroid	19.4	44.3	24.9*	51

* 15 of 16 patients showed increase of 9% or more.

In comparing the uptake values in the primary hypothyroid group with those obtained in euthyroid patients, a considerable overlap at three and five hours was evident. While there was still some degree of overlap at 24 hours, it was less than at the earlier intervals. These results suggest that the 24-hour interval provides a more reliable differentiation between the primary hypothyroid and the euthyroid patient than do the earlier intervals. Since all degrees of thyroid function occur clinically, it is inconceivable that in a representative group of patients some degree of overlap would not occur.

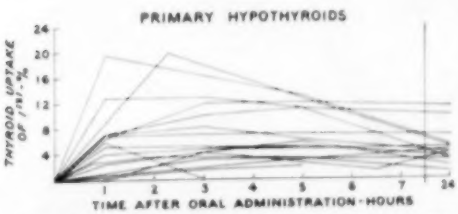

Fig. 3.—Thyroid uptake of radioiodine in 16 primary hypothyroid children.

In this group, as in the euthyroid patients, there was no correlation between age and thyroidal uptake of radioiodine.

The pre-TSH and post-TSH uptake studies, performed in nine of the primary hypothyroid patients, are presented in Figure 2 and Table 2. The average 24-hour uptake before TSH was 4.9%; this increased to 7.1% following the TSH. The average increase in uptake amounted to only 2.2%. Several patients showed no demonstrable increase, and the maximum increase was 8%.

Secondary Hypothyroid Group.—The data for the 1- to 24-hour uptake studies in the pituitary hypothyroid patients are shown in Figure 4 and Table 1. At three and five hours the uptake averaged 10.9% and 12.0%, respectively. At 24 hours the range was from 9% to 37%, with an average of 19.4%. The uptake curves in these patients rose slowly from 1 to 24 hours. In this respect the uptake curves were similar to those obtained in the euthyroid

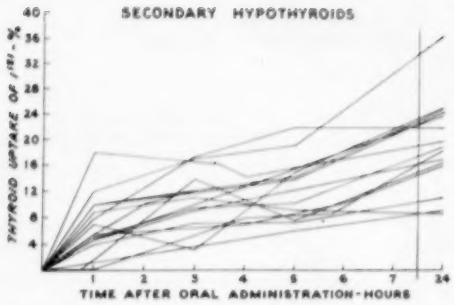

Fig. 4.—Thyroid uptake of radioiodine in 16 pituitary-hypothyroid children.

patients. In the primary hypothyroid group, however, the curves remained flat or sloped downward from one hour onward.

There was a much greater overlap between the uptake data in the secondary hypothyroid and the euthyroid groups than there was between the primary hypothyroid and the euthyroid groups. This probably reflected the fact that the degree of hypothyroidism was usually less in those with pituitary hypothyroidism than in those with primary hypothyroidism. In these patients the uptake data were of little or no value in distinguishing the mild secondary hypothyroid from the euthyroid patients.

The effect of TSH on the 24-hour uptake in the secondary hypothyroid group is shown in Figure 2 and Table 2. The average pre-TSH uptake at 24 hours was 19.4%, whereas the average post-TSH uptake was 44.3%. The minimum response to TSH was 5%, and the maximum response was 51%, with an average of 24.9%. The administration of TSH in 15 of the 16 secondary hypothyroid patients produced an increase of 9% or more; thus, 15 of the 16 showed a greater response to TSH than did any of the primary hypothyroid patients. The TSH response, therefore, is of value in distinguishing primary from secondary hypothyroidism. However, the overlap between the patients with pituitary hypothyroidism and the euthyroid patients is too great for the TSH test to be of clinical value in distinguishing between them.

In euthyroidism, primary hypothyroidism, and pituitary hypothyroidism the response of the thyroid gland to the administration of thyrotropic hormone appeared to be essentially the same in children as in adults.[7,8]

Hyperthyroid Group.—In the hyperthyroid group of patients, the three-hour uptake values showed an average of 55%, with a range from 23% to 85% (Fig. 5 and Table 1). At three hours there was only one value below 38%. These values should be contrasted with those of the euthyroid patients in whom, at three hours, there was only one value (26%) which was above 22%. The average uptake at five hours in the hyperthyroid patients was 63%, with the range from 42% to 78%. At 24 hours the average was 66%, and the range was from 48% to 79%. In the present study there was no overlap between the euthyroid and the hyperthyroid patients at 5 or 24 hours; however, it is expected that, if the series were large enough, overlap would have occurred. If reliance is to be placed on a single determination, the present data suggest that the 5- and 24-hour uptakes are of approximately equal value in differenti-

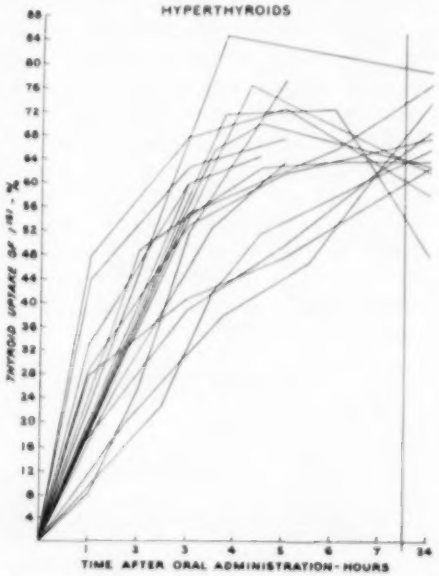

Fig. 5.—Thyroid uptake of radioiodine in 17 hyperthyroid children.

ating the euthyroid from the hyperthyroid patient. In many cases the full 24-hour uptake curve provides more information about the thyroid function than does any single point.

Summary

The 1- to 24-hour thyroidal I^{131} uptake curves of 34 euthyroid, 16 primary hypothyroid, 16 secondary hypothyroid, and 17 hyperthyroid children are presented.

The thyroid uptake appeared to be useful in distinguishing between hyperthyroidism, euthyroidism, and primary hypothyroidism. It did not separate the mild secondary hypothyroid patients from the euthyroid patients.

There was no correlation between the age of the patients and the thyroidal uptake of I^{131}.

Children with secondary hypothyroidism showed a much greater response to TSH than did those with primary hypothyroidism.

Children with secondary hypothyroidism showed a greater average response to TSH than did those who were euthyroid. However, the overlap between values for these two groups was such that in individual cases the TSH response would probably not be of clinical usefulness.

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REFERENCES

1. Martmer, E. E.; Corrigan, K. E.; Charbeneau, H. P., and Sosin, A.: A Study of the Uptake of Iodine (I^{131}) by the Thyroid of Premature Infants, Pediatrics 17:503-509 (April) 1956.

2. Van Middlesworth, L.: Radioactive Iodide Uptake of Normal Newborn Infants, A. M. A. Am. J. Dis. Child. 88:439-442 (Oct.) 1954.

3. Quimby, E. H., and McCune, D. J.: Uptake of Radioactive Iodine by the Normal and Disordered Thyroid Gland in Children: A Preliminary Report, Radiology 49:201-205 (Aug.) 1947.

4. Reilly, W. A., and Bayer, D. L.: The Value of the Measurements of Thyroid Uptake and Urinary Excretion of I^{131} in Assessing Thyroid Function of Normal and Congenitally Hypothyroid Children, J. Pediat. 40:714-721 (June) 1952.

5. Miller, E. R.; Dailey, M .E.; Holmes, A. V.; Alexander, G. I., and Sheline, G. E.: Studies with Radioiodine: I. Function and Rate of I^{131} Uptake of the Thyroid, Radiology 57:37-47 (July) 1951.

6. Pickering, D. E., and Miller, E. R.: Thyrotropic Hormone in Infants and Children: Differentiation Between Primary and Hypopituitary Hypothyroidism, A. M. A. Am. J. Dis. Child. 85: 135-140 (Feb.) 1953.

7. Perloff, W. H.; Levy, L. M., and Despopoulos, A.: The Use of Thyrotropic Hormone (TSH) in the Diagnosis of Myxedema, J. Clin. Endocrinol. 11:1495-1502 (Dec.) 1951.

8. Bishopric, G. A.; Garrett, N. H., and Nicholson, W. M.: Clinical Value of the TSH Test in the Diagnosis of Thyroid Diseases, Am. J. Med. 18:15-19 (Jan.) 1955.

Tuberculin Testing of Children by the Mother as a Step to Tuberculosis Control

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It seems generally agreed that the importance of primary tuberculosis for the control of tuberculosis has been underrated in the past.[1] Primary tuberculosis is not a benign disease; it carries a high mortality rate in the first years of life and is the source of all severe forms of tuberculosis in childhood and adult life.[2-6] Consequently, early diagnosis and treatment of primary tuberculosis is generally recognized as the most important single measure for the control of tuberculosis.[6,7]

The entire problem has received a decisive stimulus by the advent of therapeutic agents effective against the tubercle bacillus. Among them, isoniazid is the most promising and has proved to be very effective in the treatment of tuberculosis.[8,9] If present studies under the auspices of the U. S. Public Health Service confirm the value of isoniazid also in the treatment of primary tuberculosis it appears imperative to treat this disease—like other infections—in its earliest stages, where the drug may be most effective.[10]

Early recognition of primary infection is possible by tuberculin testing and roentgenographic examination. In the past two decades the value of x-ray screening has been overrated, that of tuberculin testing greatly underrated.[7] X-ray examination of the chest misses extrapulmonary infections and discovers only more advanced forms of pulmonary disease, tuberculous as well as nontuberculous; it is unsatisfactory for the early discovery of primary tuberculous infection.[11] For this purpose the tuberculin test is the most reliable, accurate, and inexpensive single test at our disposal. At the beginning of this century the majority of the population was tuberculin positive. Under these conditions x-ray screening contributed more to a tuberculosis control program than the tuberculin test; only a negative test was regarded as significant at this time. Today and in this country with decreasing frequency of positive reactors in the childhood population, the value of tuberculin testing assumes increasing importance, while x-ray screening decreases in value.

Nevertheless, tuberculin testing is still neglected even by the pediatrician.[1] It does not suffice to test every child admitted to a hospital or to use the test when tuberculous infection is suspected. Routine testing every year [12,13] is of greater value but is rarely carried out. Even if it were generally done it would still be insufficient, since about 50% of the tuberculin converters would be discovered only six or more months after their primary infection took place. This is too late for early treatment and for prevention of dissemination.[8]

Perhaps we should learn from experience with other diseases in the control of which we have already succeeded. Rickets is an instructive example. Reliable diagnostic tests and effective means for treatment and prevention have been available for a long time without the expected effect on the incidence of rickets. Nearly complete control was accomplished only after antirachitic agents were placed in the mother's hands, and through intensive education prevention of rickets was made one of the mother's daily responsibilities.

It is conceivable that a similar step would greatly enhance early diagnosis of primary tuberculosis. If tuberculin testing were left to the mother, done by her every three months throughout childhood, and the importance of this continued procedure stressed by an educational campaign, early discovery of primary tuberculosis could be accomplished. Positive reactors would have to be turned to the physician for further study and treatment.

For continuous tuberculin testing by the mother, neither Pirquet's cutaneous nor Mantoux's intracutaneous test would be feasible; the patch test would be practical.

Certain objections can be raised against such a project and have to be carefully considered. Paramount is the question of safety. Tuberculin is known to be an innocuous substance to noninfected persons, and the great majority of our childhood population today is not infected. Sensitization to tuberculin by repeated tests in noninfected persons has never been observed. The danger of focal or constitutional reactions in infected children following a tuberculin test is minimal; it increases with the dose of tuberculin absorbed into the circulation. To my knowledge, no such reactions have been described with the use of the patch test. Second in importance is the question whether the patch test is reliable enough for such a program.

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The answer was given by the American Academy of Pediatrics in a Report of the Committee on Tuberculosis: "It was agreed that the Academy ought to emphasize the importance of tuberculin testing as part of a health examination both in clinics and in private offices; that the Patch test is an excellent screening test if properly interpreted."[14]

Can mothers properly interpret the patch test, is the next question. Probably they can not unless they receive appropriate instructions by an enclosed circular. It is easy enough for a mother to comprehend that a skin which does not show any reaction two days after removal of the test means absence of infection. This will be the case in the great majority of tested children in this country. Difficulties may arise if the skin shows a reaction. Even physicians may at times have difficulties with interpretation due to insufficient experience with the test. I have dealt with this problem in a previous publication.[15] For the mothers correct interpretation of possible pseudoreactions could be facilitated by a simple instruction: that faint skin reactions present two days after removal of the test but disappearing during the following 2-3 days are of no significance. True positive reactions remain clearly visible for at least one week.

The difficulty of correct interpretation by the mother is admitted; yet it is better to err in the direction of a false positive than a false negative reaction. Subsequent retesting by the physician with a Mantoux test using 1.0 mg. of old tuberculin will correct errors. In any case of doubt, the mother should be instructed to consult her physician. Thus, an occasional misinterpretation of a skin reaction by the mother does not involve any risk.

Will mothers conscientiously apply patch tests at the recommended intervals to their children? Many mothers probably will not. It is easier for daily administrations such as that of vitamin D to develop into a daily routine with rare misses than it is for procedures to be done at longer intervals. Intensive education will definitely be necessary as it was for similar public health projects. Even if the recommended test schedule is only partially followed by a majority of mothers, great progress will have been made in the early diagnosis of primary tuberculosis.

Finally, the idea of placing a diagnostic test in the mother's hand may be opposed as an interference with the physician's domain. Tuberculin testing by the mother does not necessarily interfere with the periodic health examinations by the physician; it will rather supplement them in an important area hitherto neglected. In the common responsibility for the child's health, the ties between mother and physician will not be endangered but strengthened; the mother only assists the physician and depends on him for final diagnosis and therapy.

The cost for such a program would be negligible. The expenses could be further reduced by simplification of the patch test, using only one tuberculin square and no control; the value of the test would not be appreciably impaired by this modification.[16] Public health authorities could defray all expenses for the indigent population through health departments.

When should tuberculin testing by the mother begin and how long should it be continued? This will depend on the circumstances and will change during the course of time with the shifting frequency of primary infection to later age groups. With a known contact case in the family, testing should start at 2-3 months of age and should be continued until a positive reaction appears. As a general measure, testing should begin during the first half year of life and be continued into adolescence. This upper age limit is admittedly arbitrary. It can be more clearly defined only after years of experience with such a testing program. The accumulation of sufficient data may in due time call for modifications.

The success of such a project can not be predicted. The difficulties involved have been appreciated and stated. They can be overcome only with critical optimism and with confident determination.

Summary

Primary tuberculosis is the source of all severe forms of tuberculosis in childhood and adult life. Consequently, the most important single measure for tuberculosis control is early diagnosis and treatment of primary tuberculosis. The tuberculin test is the most reliable and inexpensive means for early discovery of primary infection. Its occasional use by the physician contributes little to the ultimate aim.

Tuberculin patch testing of all children done every three months by the mother in cooperation with the physician is suggested as a safe and reliable method for early discovery of primary tuberculosis; it would permit early treatment and prevention of dissemination. The difficulties of such a project are appreciated and discussed. If overcome by an educational campaign, such a testing program may prove to be a valuable contribution to the conventional methods of tuberculosis control.

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REFERENCES

1. Hsu, K. H. K.: Medical Progress: Should Primary Tuberculosis in Children Continue to be Neglected?, J. Pediat. 48:501, 1956.

2. Lincoln, E. M.: The Value of Follow-Up Studies of Children with Primary Tuberculosis, Am. Rev. Tuberc. 64:499, 1951.

3. Rich, A. R.: The Pathogenesis of Tuberculosis, Springfield, Ill., Charles C Thomas, Publisher, 1951.

4. Wallgren, A.: The Time Table of Tuberculosis, Tubercle 29:245, 1948.

5. Brailey, M. E.: Prognosis in White and Colored Tuberculous Children According to Initial Chest X-Ray Findings, Am. J. Pub. Health 33:343, 1944.

6. Waring, J. J.: The Current Treatment of Pulmonary Tuberculosis, Dis. Chest 25:361, 1954.

7. Myers, J. A.: Editorial: Relationship of Tuberculous Infection to Illness, Am. Rev. Tuberc. 71:885, 1955.

8. Deuschle, K.; Ormond, L.; Elmendorf, D.; Muschenheim, C., and McDermott, W.: The Course of Pulmonary Tuberculosis During Long-Term Single-Drug (Isoniazid) Therapy, Am. Rev. Tuberc. 70:228, 1954.

9. Lincoln, E. M.: The Effect of Antimicrobial Therapy on the Prognosis of Primary Tuberculosis in Children, Am. Rev. Tuberc. 69:682, 1954.

10. Schaeffer, W. B.: The Effect of Isoniazid on Growing and Resting Tubercle Bacilli, Am. Rev. Tuberc. 69:125, 1954.

11. Myers, J. A.; Diehl, H. S.; Boynton, R. E., and Horns, H. L.: Tuberculosis in Physicians: Chairman's Address, J. A. M. A. 158:1, 1955.

12. Gray, W. C.: Mass Tuberculin Patch Testing of School Children, J. A. M.A. 158:8, 1955.

13. Feldmann, F. M.: The Tuberculin Test, Tuberc. Absts. 29: No. 4 (April) 1956.

14. Lincoln, E. M.: Report of Committee on Tuberculosis, Pediatrics 16:280, 1955.

15. Vollmer, H.: Pseudoreactions to the Tuberculin Patch Test, Am. J. Dis. Child. 78:302, 1949.

16. Vollmer, H., and Lyons, D. R.: Simplified Transparent Tuberculin Patch Test, A. M. A. Am. J. Dis. Child. 81:541, 1951.

Tuberculosis Case Finding in the Preschool Population

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The need for a practical method of tuberculosis case finding among children has long been felt. The photofluorogram, widely accepted for case finding among adults, has so far not proved applicable to children. Previous studies suggest that the tuberculin patch test (Vollmer) might be extremely valuable for this purpose.

Mortality statistics, morbidity reports, autopsy examinations, tuberculin tests, and x-ray surveys indicate that about one-half of all infected persons develop clinical tuberculosis and that from 10% to 20% of these eventually die of the disease.[1] Myers[2] followed 8-year-old children with positive tuberculin tests, along with a control group, for 14 years and found tuberculosis developing eight times as much in the positive reactors.

The present study was planned to investigate the usefulness to a general medical service agency of the tuberculin (Vollmer) patch test as a case finding device in an area where tuberculosis is highly endemic.

The Home Medical Service, a joint activity of the Massachusetts Memorial Hospitals and Boston University School of Medicine, has for many years provided medical service to the indigent and medically indigent in Boston.[3] The role of this agency in the teaching of medicine and related social sciences has been previously described.[4,5]

The service area is roughly one square mile. It contains about 58,000 persons of varied racial background, many of whom are in poor economic circumstances. About 2000 patients are attended yearly. Sixty per cent of these are under the age of 9; fifty per cent are under the age of 4.

The South End of Boston, which makes up a large part of the Home Medical Service area, has had an unusually high tuberculosis mortality rate for many years. Recently, along with the country-wide trend, the rate decreased to 88.0 per 100,000 in 1954, but the new case rate has remained essentially stationary at 306.7 per 100,000. By contrast, the death rate in 1954 for the remainder of the city was 18.1; the new case rate, 71.9.[6]

The age distribution, the wide acceptance of the Service activities, and the high endemicity of tuberculosis seemed to make a favorable situation for such a study. It was accordingly planned to apply the patch test during the course of home visits to all children who had not reached their fifth birthday.

This age group was selected because the children would be available, at home, for the reading of the tests and because their contacts with tuberculosis might be expected to be few in number and recent in occurrence.

In tuberculosis control, discovery and follow-up of reactors is as important as the investigation of contacts.[1] Rathburn has underscored this importance in his finding a background of primary tuberculosis in about 75% of adolescents with reinfection type disease.[7]

Method

The Vollmer Patch Test (Lederle Co.) was used because of the easy portability of the test materials, the simplicity of application, the absence of constitutional reactions, the minimal danger of local infection, and the acceptance by the children of a test in which needles are avoided. Against these factors must be weighed the disadvantages of missed cases. Other possible disadvantages of the patch test, such as reactions to the adhesive, local reactions such as vesiculation, itching, and shallow ulcers, and premature re-

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TABLE 1.—*Reported Experience with Mantoux and Patch Tests*

Author	Number of Tuberculous Subjects	Number of Positive Patch Tests	Positive Patch Tests (per Cent)	Number of Positive Mantoux Tests	Positive Mantoux Tests (per Cent)	Comment
Vollmer and Goldberger[14]	209	207	99	207	99	Patch tests read at 72 hours
Vollmer and Goldberger[11]	169	165	97.6	165	97.6	Patch tests read at 72 hours; P.P.D. used for Mantoux
Steward[15]	96	96	100	90	93.7	1:1000 O.T. for Mantoux
Vollmer[13]	37 535	36 529	97.3 98.8	36 530	97.3 99.0	Patch tests read at 72 hours
Narodick[14]	332	328	98.7	330	99.7	
Brock and Schnatz[16]	41	38	95.1	38	95.1	Patch tests read at 72 hours; 1:1000 O.T. for Mantoux
Diddy[16]	129	----	----	----	----	Reported 98.8% conformity of patch and Mantoux tests; 1:1000 O.T. for Mantoux
Dormer et al.[17]	194	184	94.8	184	94.8	
Corper[8]	64	58	90.6	62	96.8	
Bell and Jerram[18]	58	31	53.4	58	100	Patch tests read at 48 hours

moval by the patient, were trivial in our experience.

Studies of the results obtained with the patch test are difficult to compare because of varying techniques (site of application, preparation of skin, time and criteria of reading) and differences of the age groups tested. The Mantoux test has generally served as the standard against which the performance of the Vollmer patch has been measured, but the variation in sensitivity encountered in the use of the Mantoux under practical conditions suggests the need for a more rigid primary standard, namely, proved tuberculous state. Studies on known tuberculous subjects are presented in Table 1. In patients with active tuberculosis, the two tests correlate very well (90.6% to 100%), except in one study[8] where the tests were read at the end of 48 hours.

Our final method and criteria, developed from the findings of previous studies, were as follows: During the course of a home visit made to a household by reason of illness of any one of its members, the extern tested all children under the age of 5. The skin of the midscapular area was prepared with acetone and the patch applied. The mother or guardian was instructed to remove the patch at the 48th hour, and the results were interpreted by one of us at about the 96th hour.

Those reactions were considered to be positive which, in the face of a negative control area, presented induration with or without redness, or any degree of papulation or vesiculation. No attempt was made to grade the reactions.

Follow-Ups of Positive Reactors

Arrangements were made with the Pediatric Out-Patient Department of Boston City Hospital for the performance of intracutaneous tuberculin tests, chest films, and other follow-up care. Parents and older siblings, the likeliest contacts, were referred to the local Health Units of the Health Department of the City of Boston.

Results

In all, 826 Vollmer patch tests were applied, of which 804 (97%) were read. This represented tuberculin testing of about 16% of the 5000 persons composing the 0-5-year-old population of the Service area.[9] The unread tests reflect difficulties in contacting these patients at the proper time. Each patient unavailable at the proper time was revisited on two successive days; this led to 11 (1.3%) patch tests being read at the 120th rather than the 96th hour. Seventeen (2.1%) of the test patches were removed before 48 hours, while twenty-six (3.1%) were left in place for 72 to 96 hours. The single positive reaction among these overtime patches was also positive to an intracutaneous P. P. D. test. The age, sex, and racial distribution of the subjects is presented in Table 2.

Positive reactions were obtained in 41 patients, or about 5% of the study group. There were two questionable reactions with only erythema and puffiness. These will be

TABLE 2.—*Age, Sex, and Race Distribution of Total Study Group and of Positive Patch Test Reactors*

	Age, Years					Sex		Race	
	0-1	1-2	2-3	3-4	4-5	Male	Female	White	Nonwhite
Study group	189	141	162	170	164	425	401	360	466
Positive reactors	4	2	8	14	13	19	22	20	31

discussed below. Table 2 also presents the age, sex, and racial distribution of the positive reactors. Thirteen of these patients had been exposed to tuberculosis; these constituted 31.7% of the 67 contacts in the study. The geographical distribution of the reactors corresponded to the areas of greatest population density.

Follow-up was not possible on 3 (7.3%) of the 41 positive reactors because of removal beyond the Service area. Six patients were not subjected to P. P. D. intracutaneous tests, four of these because of severe reactions to the patch tests. Thirty-two P. P. D. tests were done either in the Out-Patient Department or in the home by one of us (J. D. C.). Nineteen of these tests were positive (induration 5×5 mm. or more). These are listed in Table 3. Some children received only first strength tests because of loss of contact.

TABLE 3.—*Mantoux (P.P.D.) Reactions Among Positive Patch Reactors*

P.P.D. Strength	Positive	Negative
First	4	3
Intermediate	7	0
Second	8	10

Full-size chest films were obtained on 35 of the 41 positive patch reactors. Interpretations were made by roentgenologists of the Boston City Hospital or the City Health Department. Twelve of these films were considered to be consistent with the diagnosis of possible or probable tuberculosis. The data on these cases are presented in Table 4.

A 2-year-old white boy with a honeycombed appearance of the right lower lung field, considered to be pneumonitis, is not included. A first strength P. P. D. test on this child was negative, and he moved from the state before work-up could be completed.

Second-strength P. P. D. tests were carried out on the two questionable patch-test reactors mentioned above. One child had a positive reaction; his chest film was negative. The second child was negative to intracutaneous test and to chest x-ray. The positive reaction in the first child whose Vollmer patch had been interpreted as questionable suggests that it may be good procedure to investigate any child who shows the slightest reaction to the patch test. This opinion had been advanced previously by Court,[25] Hudson, and Hytten.[26]

Comment

Eight hundred twenty-six tuberculin patch tests uncovered one case of active tuberculosis, seven cases of probable and three cases of possible disease. A group of 30 other children were identified by reason of tuberculin reactivity and will be closely followed because of their greater risk.[1] Through these children two adults with active tuberculosis were found and hospitalized.

Positive patch tests in the face of negative intracutaneous tests cannot be disregarded. Some studies [8,11,18,19] have reported similar findings in children with probable or proved tuberculosis. A few workers [20-22] would consider these reactions to be false positives, but there appears to be little basis for this opinion. Vollmer [23] has pointed out that he has seen only 11 pseudoreactions in his 10-year experience with the test. For this reason, most of the positive reactors are still being followed. Many of the patients with probable disease uncovered by

TABLE 4.—*Summary of Data on Children Showing Clinical Evidence of Disease*

Patient	Race	Sex	Age, Yr.	Skin Tests		X-Ray	Contact History	Remarks
				Vollmer	Mantoux			
						Group I—Active Tuberculosis		
1	W	M	3	Pos.	*		Father	A rediscovery of patient known to Health Department; bilateral apical disease; not included in this series
2	W	F	2½	Pos.	Not done	Jan. 18, 1956; diffuse infiltrations about both hilar regions	None	Mother studied and found to have active pulmonary tuberculosis; child died within a month of take-up; postmortem revealed caseous tuberculosis of right lung with hematogenous spread, and meningococcus meningitis
						Group II—Probable Tuberculosis		
3	N	M	4	Pos.	Pos. 1½	Jan. 13, 1956; rounded density, right hilus, probably lymph nodes of tuberculosis	Mother	Serial x-rays revealed central pneumonic process in right hilus consistent with primary complex
4	W	M	4	Pos.	Pos. 1	Feb. 8, 1956; generally increased linear markings, thickening of hilar shadows; rounded, lobulated shadows, left hilus consistent with lymph-node enlargement	None	
5	N	F	4	Pos.	Pos. 1½†	Dec. 4, 1955; increased density middle and upper fields of right lung Jan. 20, 1956; emphysema, right upper lung field, thickening of interlobar fissure with patchy density at right paracardiac region	Grandmother	Two siblings presented positive patch tests but were negative on chest x-ray
6	N	F	2½	Pos.	Pos. 2½†	Jan. 5, 1956; irregular thickening about left hilus associated with questionable small areas of calcification	None	
7	W	M	1½	Pos.	*	Oct. 10, 1955; lobulated area of increased density about the right hilus	Mother	Mother was in sanitorium at time of study
8	W	F	3	Pos.	*	Feb. 1, 1956; infiltration right upper lobe with increased markings and a smooth curvilinear density in left hilus	None	
9	W	F	2	Pos.	Pos. 1½	Feb. 17, 1956; increased density extending into right apex from paracardiac region; increased density extending from left hilus toward lung periphery	None	
						Group III—Possible Tuberculosis		
10	N	M	6/12	Pos.	Neg. 2†	May 8, 1956; linear infiltrations about both hilar regions	None	
11	N	F	4½	Pos.	Neg. 2†	March 13, 1956; right hilar prominences suggestive of lymph nodes	None	
12	N	F	3	Pos.	Neg. 2†	March 14, 1956; left hilar prominence suggestive of lymph nodes	None	Sibling of Patient 11, supra

* Marked skin reaction to Vollmer; Mantoux not done.
† P.P.D. strength designation: 1—first strength; 1½—intermediate strength; 2—second strength.

this study have been included in an investigation of the treatment of primary tuberculosis and will be assured of adequate medical supervision.

This study compares well with a recent survey of an older age group in the St. Louis schools reported by Gray.[24] Of 1395 patch-test reactors among the 15,755 students and their contacts tested, 13 active and 12 suspected cases of tuberculosis were found.

The total cost of our study was approximately $110.00, exclusive of personal costs. This included $50.00 for patch tests and $60.00 for transportation. The cheapness of this case finding method, in an area highly endemic for tuberculosis and with a large preschool population, as compared with photofluorogram surveys is apparent.[24]

Despite the general activity of the Home Medical Service, which in some months reached 2000 home visits, the addition of the patch testing routine was in no way burdensome. The patch test as a case finding device would appear to be especially useful to medical facilities handling large numbers of persons. There are difficulties, however, which merit statement.

The foremost problem encountered was population mobility. Eight families, involving 10 reactors, moved during the study (less than one year); three of these now live in another state. Despite adequate instruction, there was a tendency for the subject to be out when the physician called to read the test. Anxiety appears to augment this tendency. In one family with two positive reactors it appeared that an active effort was being made to avoid the reading. Intradermal tests were found very difficult to perform in the home situation even with the aid of a nurse. Children are very sensitive to the sight of a needle, particularly with the widespread use of painful depot penicillin preparations. In general, the mothers accepted and cooperated well with the patch test itself. Some reluctance was evident, however, in the routine follow-up of positive reactors where, in isolated instances, several visits were required to secure action on x-rays and clinic visits.

This experience suggests strongly that Vollmer patch testing should be required on all children entering nursery and primary schools in areas of high tuberculosis endemicity. If the criteria of a positive skin test are broadened to include any reaction whatsoever of the test areas which is not present in the controls, then this procedure might well be carried out by the public health nurse or the school teacher under medical supervision. A potent case finding device would, in this manner, be applied to a considerable population at risk.[27]

Summary

The Vollmer patch test was employed by a medical service facility as a routine device for finding cases of tuberculosis in the 0-5-year-old population of an area with high tuberculosis endemicity. Eight hundred four persons, comprising about 16% of the area's 0-5-year-old population, were tested. Forty-one positive reactions were encountered leading to the recognition of one active, seven probable, and three possible cases of tuberculosis. The usefulness, cheapness, and wide applicability of the patch test is indicated.

Dr. Herbert J. Kaufmann, of the Boston City Hospital Pediatric Out-Patient Department, cooperated in this study.

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REFERENCES

1. Bogen, E.: The Toll of Tuberculous Infection, Am. Rev. Tubere. 42:253-258, 1940.

2. Myers, J. A., and Harrington, F. E.: The Effect of Initial Tuberculosis Infection on Subsequent Tuberculous Lesions, J. A. M. A. 103: 1530-1536, 1934.

3. Bakst, H. J.: Domiciliary Medical Care and the Voluntary Teaching Hospital, Am. J. Pub. Health 43:589-595, 1953.

4. Bakst, H. J.: A Domiciliary Medical Care Program as an Integrated Facility in Medical Curriculum, J. Am. M. Coll. 25:406-416, 1950.

5. Stone, B. S., and Bakst, H. J.: Educational Experience in Social Work and Medicine on a

Domiciliary Medical Care Service, Soc. Serv. Rev. 26:42-52, 1952.

6. Boston's Health Statistical Summary, 1954.

7. Rathburn, W. L.: Epidemiological Basis for the Control of Tuberculosis Among Children, Nat. Tuberc. A. Tr. 15:278, 1929.

8. Corper, H. J.: Comparative Results with Transdermal and Intracutaneous Tuberculin Tests, J. Lab. & Clin. Med. 29:378-403, 1944.

9. U. S. Bureau of Census: U. S. Census of Population: 1950, Vol. 3, Census Tract Statistics, Washington, D. C., U. S. Government Printing Office, 1952.

10. Vollmer, H., and Goldberger, E. W.: A New Tuberculin Patch Test, Am. J. Dis. Child. 54:1019-1024, 1937.

11. Vollmer, H., and Goldberger, E. W.: Comparative Study of the Tuberculin Patch Test and the Mantoux Intracutaneous Test, Am. J. Dis. Child. 56:584-586, 1938.

12. Steward, W. D.: The New Tuberculin Patch Test, J. Pediat. 13:510-512, 1938.

13. Vollmer, H.: Value of the Tuberculin Patch Test in Case Finding, J. Pediat. 16:627-636, 1940.

14. Narodick, P. H.: The Tuberculin Patch Test, Northwest Med. 41:193-196, 1942.

15. Brock, H. J., and Schnatz, F. T.: A Comparison of the Tuberculin Patch Test with the Mantoux Test, New York J. Med. 42:1241-1242, 1942.

16. Diddy, G. A.: Patch Test: Its Evaluation, California & Western Med. 59:60-61, 1943.

17. Dormer, B. A.; Friedlander, J.; Wiles, F. J., and Schaffer, R.: Tuberculin Patch Test: Comparison with Mantoux Intracutaneous Test, Am. Rev. Tuberc. 48:324-328, 1943.

18. Bell, D., and Jerram, U.: Tuberculin Testing in Children, Brit. M. J. 2:215-216, 1945.

19. Colebatch, J. H.: The Tuberculin Patch Test, M. J. Australia 2:640-645, 1941.

20. Neiman, I. S., and Loewinsohn, E.: Tuberculin Patch Test: Screening Procedure to Discover Tuberculin Reactors in Children, Am. Rev. Tuberc. 55:495-497, 1947.

21. Pascher, F., and Sulzberger, M. B.: Tuberculin Patch Test and Mantoux Test: Comparative Study in Cases of Various Dermatoses, Including Tuberculoderms, Arch. Dermat. & Syph. 49:256-259, 1944.

22. Weiner, S. B., and Neustadt, A.: Tuberculin Patch Test, J. Pediat. 14:752-754, 1939.

23. Vollmer, H.: Pseudoreactions to the Tuberculin Patch Test, Am. J. Dis. Child. 78:302-305, 1949.

24. Gray, W. C.: Mass Tuberculin Patch Testing of School Children, J. A. M. A. 158:8-10, 1955.

25. Court, D.: A Comparative Study of the Tuberculin "Patch Test" and the Intracutaneous Mantoux Test in Childhood, Brit. M. J. 1:824-826, 1939.

26. Hudson, C., and Hytten, F. E.: The Tuberculin Patch Test: A Comparison with the Mantoux Test, M. J. Australia 1:475, 1946.

27. Myers, J. A.; Gunlaugson, F. G.; Meyerding, E. A., and Roberts, J.: Importance of Tuberculin Testing of School Children—A 28 Year Study, J. A. M. A. 159:185-190, 1956.

Phenylketonuria

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Recently acquired knowledge and increased interest in the problems of mental retardation have prompted this presentation on phenylketonuria. Twenty-one patients are reported with a review of the literature. Phenylketonuria may well become a working model for the study of diseases in which psychological abnormalities and multiple biochemical aberrations are the result of a genetically determined enzyme deficiency.

History

The Norwegian biochemist Fölling first described phenylketonuria in 1934.[1] He isolated and crystallized phenylpyruvic acid from the strikingly malodorous urines of two defective siblings. Later, he reported 10 similar patients, noting the lack of clear-cut physical characteristics, a tendency toward dermatoses, muscular rigidity, and an ape-like, or pithecoid, posture. Since phenylpyruvic acid was not found in the urine of normal persons, he related its presence to the mental retardation and named the disease "Imbecillitas Phenylpyruvica." Cases were identified in other European countries and America,[2-4] and by 1954 Jervis found 513 recorded cases in the literature.[5] Earlier he had suggested the term "phenylpyruvic oligophrenia," although a more appropriate term, "phenylketonuria," was suggested by Penrose[2,58] because of the presence of the ketonic acid, phenylpyruvic acid, in the urine. General reviews on the subject have been presented by Cowie,[6] Penrose,[7,8] and Jervis.[5]

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Case Material

Since 1954, every patient at Pacific State Hospital, a California institution for the mentally retarded, has been tested for the presence of phenylpyruvic acid in the urine, using the standard $FeCl_3$ test. The dinitrophenylhydrazine test for keto acids has been used for confirmatory evidence. The patient material included approximately 3000 patients, representing all degrees of mental defect and ranging in age from 1½ to 65 years. Twenty-one phenylketonurics were found. Table 1 lists them by age, sex, I. Q., admission diagnosis, reason for admission, and family history.

Clinical Findings

The clinical signs described by other authors[1-22,100] may be grouped as follows: mental defect, neuromuscular abnormalities, behavioral deviations, and somatic changes.

A review of our case histories shows that mental retardation was usually diagnosed early in life, in only one case as late as school age (Case 21). Chief complaints did not differ from those observed in other patients with mental retardation. They included delay in sitting, walking, talking, and generally slow motor and mental development. The presence of seizures in early infancy was the first sign in two patients. None of the parents complained of an unusual odor of the urine, and this sign was observed by us in only two cases. One patient suffered from severe eczema which was controlled by diet. All patients had a preadmission diagnosis other than phenylketonuria; the three who were correctly diagnosed prior to admission had been examined on an outpatient basis by the hospital staff (Table 1).

Most authors have noted that the degree of mental defect is severe. The I. Q. is usually less than 20. Table 2 tabulates the distribution of intelligence quotients in 362 phenylketonurics in the literature, including

TABLE 1.—*Basic Data on Twenty-One Cases of Phenylketonuria*

Case No.	Age*	Sex	I.Q.†	Admission Diagnosis	Reason for Admission	Family History‡
1	17	F	?‖	Birth injury	Hyperactive	Negative (1)
2	10	M	4	Undifferentiated	Nursing care	Negative (3)
3	26	F	6	Cerebral palsy	Nursing care	Negative (0)
4	36	M	7	Postmeningitis	Hyperactive	Negative (4)
5	24	M	8	Birth injury	Hyperactive	Sibling, Case No. 21 (0)
6	28	F	9	Birth injury	Hyperactive	Negative (1)
7	21	F	9	Familial	Nursing care	2 sibs defective (2)
8	11	F	9	Undifferentiated	Aggressive	Parents 3rd cousins (2)
9	9	M	11	Undifferentiated	Hyperactive	Negative (0)
10	9	M	15	Hydrocephalus, mild	Hyperactive	Negative (1)
11	43	F	17	Psychosis	Nursing care	Mother psychotic (0)
12	10	F	18	Birth injury	Hyperactive	Negative (4)
13	6	M	20	Phenylketonuria	Hyperactive	Parents 1st cousins (2)
14	2	F	23	Phenylketonuria	Hyperactive	Negative (1)
15	7	F	32	Phenylketonuria	Hyperactive	Sibling, Case No. 19 (0)
16	6	F	32	Undifferentiated	Behavior problem	Negative (0)
17	5	F	35	Undifferentiated	Behavior problem	Negative (1)
18	25	F	33	Undifferentiated	Behavior problem	Twin, Case No. 20 (1)
19	5	M	40	Schilder's disease	Hyperactive	Sibling, Case No. 15 (0)
20	25	F	49	Undifferentiated	Behavior problem	Twin, Case No. 18 (1)
21	29	M	64	Familial	Hyperactive	Sibling, Case No. 5 (0)

* As of Jan. 1, 1956.
† Kuhlman-Binet, Stanford-Binet L, and Wechsler-Bellevue T, depending on mental development of patient.
‡ Refers to type of mental deficiency.
§ Family history includes only parents and siblings. The number of normal siblings is indicated in parentheses; their urines were not tested for phenylpyruvic acid.
‖ Could not be tested. Estimated social quotient 28.

TABLE 2.—*Distribution of Intelligence Quotients in 362 Phenylketonurics**

	I.Q. 1-20	I.Q. 21-50	I.Q. 51-70	I.Q. Above 70
Number	229	115	15	3
Per cent	63	32	4	1

* Adapted from Jervis (Reference 5). Includes 11 patients reported by Armstrong (Reference 55) and 21 by us.

our own cases. Two-thirds had an I. Q. below 20; ninety-five per cent had I. Q.'s below 50. Younger patients in our experience show relatively higher I. Q.'s because tests rely on less impaired neuromuscular abilities.

There are patients reported in the literature with relatively high intelligence quotients. Cowie [6,9] described a 7-year-old boy with few of the physical signs, a reduced output of phenylpyruvic acid and a Binet I. Q. of 76. Jervis cited three patients with I. Q.'s above 70, one with an I. Q. of 98.[5] Investigators have found no correlation between the I. Q. and the quantity of phenylpyruvic acid excreted.[55,57,63] There may not be a sharp distinction between the mentality of the normal and the phenylketonuric person,[10,22] and the possibility exists that a number of patients remain unrecognized in the general population because of a relatively adequate intelligence.

Neurological findings are summarized in Table 3. The presence of seizures has been noted by most authors and Jervis reported them in 25% of his cases.[3] They were present in 9 of our 21 patients and were usually of the grand mal type. Seizures started at different ages, most commonly during the first two years of life. In some instances they lasted less than a year; in others they continued through adulthood (Cases 3 and 5). Seizures were difficult to control.

Increased knee reflexes were common, particularly in our older children and adults. The Babinski reflex was not present. Short-stepped gait, pithecoid stance, and increased muscle tone were present to a variable de-

TABLE 3.—*Neurological Findings in Twenty-One Patients with Phenylketonuria*

Signs	Present In
Increased muscle tone	16
Increased knee reflexes	14
Unable to walk	3
Short-stepped gait	11
Pithecoid stance	4
Positive Babinski reflex	0
Seizures	9
Absent speech	15
Limited speech	3
Abnormal eye grounds	1

TABLE 4.—*Behavioral Findings in Twenty-One Patients with Phenylketonuria*

Signs	Present In
Impaired awareness	15
Fright reaction	11
Digital mannerisms	8
Echopraxia	3
Catatonic signs	2
Echolalia*	1
Untidiness	13

* Only six patients could speak.

gree, whereas typical athetoid movements, retro- and anteropulsion were not noted by us. Speech was normal in three of the patients; all were adults and had the highest I. Q.'s. In three other patients it was limited to a few indistinct words, and in 15 it was completely absent. All but three of the patients were able to walk. The appearance of speech and the ability to walk usually coincided within a year. If a child had not learned to speak by the age of 5, no speech developed later. Deafness was not noted by us or others.[94]

In one patient funduscopic examination revealed pale eye grounds with poor vascular pattern described by the ophthalmologist as being "albino in character." The others had normal fundi. Thinning of the retina with poor choriocapillaries and pale nerve head, as well as normal findings, have been described.[11,6]

The behavioral deviations noted in our patients are summarized in Table 4. Other authors have noted emotional instability, catatonic-like posturing, apathy, stupor, aggressiveness, temper tantrums, automatic movements, and schizophrenic outbursts. The general behavior in several of our patients showed a marked deviation from that of other defective children. None could be described as friendly, placid, or happy. The commonest finding was an impaired awareness of surroundings, with a failure to respond even to strong stimuli. Some patients were completely inaccessible to the examiner. Severe fright reactions were common. Digital mannerisms were frequent; they were slow, methodical, and stereotyped, or rapid and purposeless. Less frequent symptoms included echolalia, perseveration, echopraxia, and catatonic posturing. Progressive deterioration did not occur in any of our patients following admission to the institution, nor was it noted by others.[3,13]

The reasons for admission to the institution are given in Table 1. Most of the patients came because their hyperactive behavior, irritability, episodes of screaming, noisiness, uncontrollable temper tantrums, and general untidiness placed a heavy physical and emotional burden upon the parents and siblings. Only a few were toilet trained at the time of admission. In several cases improvement was noted after admission, suggesting that environmental factors at home may have aggravated the unacceptable behavior.

Additional physical signs are noted in Table 5. The characteristic dilution of the hair, eye, and skin color mentioned by many authors was absent in several cases. Had they been compared with their normal siblings, the dilution in color might have been more apparent.[14] Adults tended to show better pigmentation.[101] There was no correlation between the degree of mental defect and the skin, hair, or eye color.

Dermatoses were often related to poor personal hygiene and generally responded well to local therapy. There were three patients with dermatitis factitia. A susceptibility to sunburn has been reported, although several of our adult patients showed a good degree of tanning. Other abnormalities in our series, also noted by other au-

TABLE 5.—*Other Physical Findings in Twenty-One Patients with Phenylketonuria*

Signs		Present In
Skin:	Fair	16
	Normal color	5
Eyes:	Blue	13
	Brown or hazel	8
Hair:	Blonde	10
	Brown	11
Widely spaced incisors		8
Acrocyanosis		4
Dermatitis factitia		3
Sun tan		3

thors, include the wide spacing of incisor teeth and acrocyanosis. We did not find significant degrees of diminished head circumference or dwarfing. When the measurements of height and weight for the children were plotted on Wetzel growth charts, there was a random scatter between the 2% and the 98% auxodromes. There was no indication of a delay in onset of puberty in either sex or any changes in secondary sexual characteristics. Menstruation was normal in the females.

Incidence

Many investigators have studied the frequency of phenylketonuria in institutions for the mentally defective.[3,4,6,11,12,15,16,18,19,21,24-26,29,109] Figures range from a low of 0.06% in Switzerland[4] to 2.71% in one English study.[6] Considerable variation exists even within countries which may depend on the patients studied. Case material with a high proportion of severe defect will reveal a higher incidence of the disease. Tables compiled by Jervis from the literature indicate a prevalence of 0.64% among 48,536 institutionalized mental defectives tested.[5]

All races and nationalities are affected, although only a single case has been reported in a Negro and two cases have been reported in patients of Jewish ancestry[30,31,103]; cases have been reported from Japan and India.[107,108] All of our patients were Caucasian (one was a Mexican child, Case 8). The frequency of the disease has been estimated between 2 to 6 persons in 100,000 population.[24-26] A frequent figure used is 4 per 100,000. This places the frequency of the heterozygous carrier at 1 in 80, i. e., 1.26% of the population carries the gene.[24-26]

By the most conservative estimation (2/100,000), the number of phenylketonuric persons in the United States would be about 3200. The public institutions for mental defectives and epileptics have a population of approximately 130,000.[33] Assuming by generous estimation that 1% of these patients are phenylketonuric, there are 1300 in the institutions and 1900 elsewhere! The size of this latter group suggests that many may be among the unexamined, less retarded, the psychotic, or the normal population. Larson found two instances of phenylketonuria among 1277 morons (0.16%); one of them supported a family of five.[26] A study of 8220 normal persons revealed no instances of phenylketonuria.[100]

The psychotic behavior in some of these patients suggests that phenylketonurics might be present among the mentally ill populations. Levy and Perry[15] found two instances of phenylketonuria among 1850 mentally ill patients (0.1%). Both were described as "propfschizophrenics" (mental retardates with an engrafted schizophrenic process). A recent investigation of 4246 adult psychotics revealed no phenylketonurics.[91]

Genetics

Fölling recognized early that phenylketonuria had a familial character, since 2 of his 10 patients had affected siblings.[1,29] A simple recessive mode of inheritance was suggested by Penrose[23] and demonstrated in Jervis's excellent study of 213 phenylketonurics.[24] The corrected ratio of normal to affected persons, the increased rate of consanguinity, and the low rate of appearance among collateral members of the family suggested the effect of a single recessive gene. Later studies by Penrose[7] and Munro[25] confirmed these findings. The sex distribution is equal.[5]

A 5% to 14% frequency of consanguinous marriages has been found among parents of phenylketonurics.[23-26,29] There were two consanguinous marriages in our case material—one involved first cousins and the other third cousins.

Several instances of matings involving a phenylketonuric have been reported with affected offspring[3,5,30] and with normal children.[5,16,26] Jervis reported three sets of twins, one monozygotic and concordant and

TABLE 6.—*Frequency of Phenylketonuric Offspring in Various Matings**

Marital Partners				Theoretical Frequency of Affected Children if Both Partners Were Carriers	Chances of Affected Children from Such a Mating
A		B			
Carrier Status	Chances of Carrying Gene	Carrier Status	Chances of Carrying Gene		
Unknown	1/80	Unknown	1/80	1/4	1/25,600
Unknown	1/80	Sibling of phenylketonuric	2/3	1/4	1/480
Unknown	1/80	Parent of phenylketonuric	1	1/4	1/320
Unknown	1/80	Phenylketonuric	1	1/2	1/160
Sibling of phenylketonuric	2/3	Sibling of phenylketonuric	2/3	1/4	1/9
Sibling of phenylketonuric	2/3	Parent of phenylketonuric	1	1/4	1/6
Sibling of phenylketonuric	2/3	Phenylketonuric	1	1/2	1/3
Parent of phenylketonuric	1	Parent of phenylketonuric	1	1/4	1/4
Parent of phenylketonuric	1	Phenylketonuric	1	1/2	1/2
Phenylketonuric	1	Phenylketonuric	1	1	1

* Calculated on prevalence rate of disease as approximately 4/100,000, as suggested by Jervis (References 5 and 25).

the others dizygotic, with one pair concordant and the other discordant.[24] In our series there was one set of twins (Cases 18 and 20). Despite physical differences they are concordant, and blood typing suggests monozygosity.

The importance of genetic counseling is evident from Table 6, which indicates the chances of phenylketonuric children from various matings. Attention is directed to the fact that the birth of a phenylketonuric places the parents in the category of known carriers and considerably alters the eugenic prognosis. Table 6 concerns itself only with the phenylketonuric, his immediate family, and the person whose carrier status is "unknown."

Genetic estimates can be made also for distant relatives. These are not included in Table 6 for reasons of brevity but would fall into the mid range of probabilities. Uncles or aunts of phenylketonurics have a one-half probability and cousins a one-fourth probability of being heterozygous carriers. It should be apparent that marriages between relatives of phenylketonurics are to be discouraged. Sterilization of the recognized phenylketonuric accomplishes little from a eugenic standpoint because of the high frequency of the unrecognized heterozygotes.[7]

Several clinical and biochemical studies have been conducted in an effort to detect the heterozygous carrier. A high frequency of mental diseases among relatives of phenylketonurics has been observed by some authors.[7,15,23,24] Our findings as well as those of others have not confirmed this

TABLE 7.—*Phenylalanine and Tyrosine Derivatives in Plasma and Urine of Normal and Phenylketonuric Persons*

	Blood		Urine	
Substance	Normal	Phenylketonuric	Normal	Phenylketonuric
Phenylalanine	1-2 mg/100 cc.	15-63 mg/100 cc.[27,34,41]	0.03 gm/day[39]	0.3-1 gm/day[27,33,38,42,44]
Phenylpyruvic acid	Absent	0.3-1.8 mg/100 cc.[41]	Absent	0.3-2 gm/day[4,27,33,41]
Phenyllactic acid	Absent	Absent[33]	Absent	0.29-.55 gm/day[33,39,41]
Phenylacetic acid	Absent	Small amounts[4]	Absent	Increased[41]
Phenylacetylglutamine	Not reported	Not reported	0.2-0.3 gm/day	2.4 gm/day[27,39]
Tyrosine	Normal	Normal[33]	Normal	Normal
Parahydroxyphenylpyruvic acid	Not reported	Not reported	Absent	Increased[41,42]
Parahydroxyphenyllactic acid	Not reported	Not reported	Absent	Increased[41,42]
Parahydroxyphenylacetic acid	Not reported	Not reported	Absent	Increased[41,42]
Orthotyrosine	Not reported	? increase[42]	Absent[41]	Absent[41]
Orthohydroxyphenylacetic acid	Not reported	Not reported	1 mg/day	100-400 mg/day*[42]

* Expressed as milligrams per gram of creatinine.

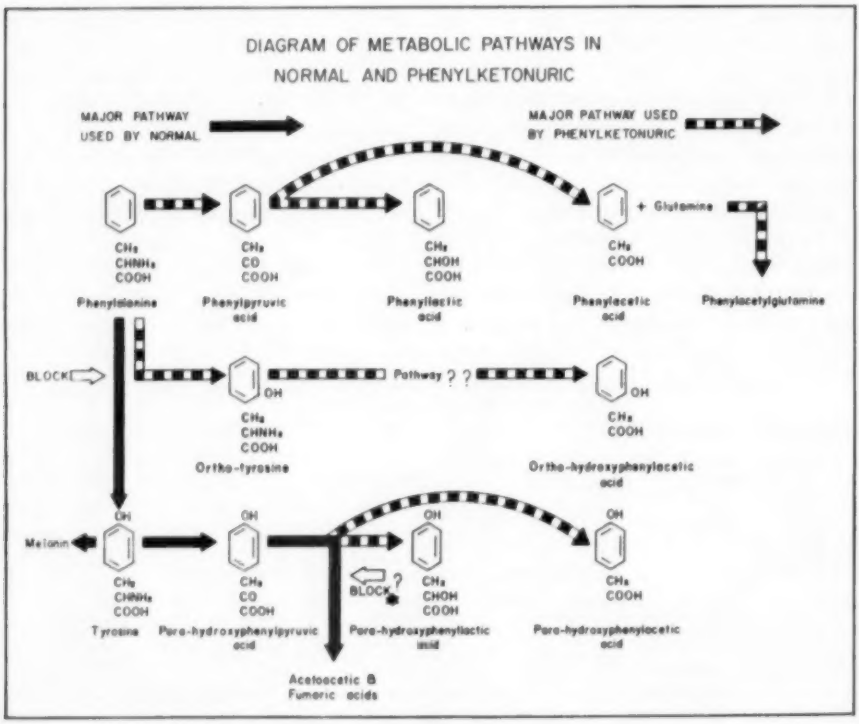
fact.[6,16,25] Biochemical studies on family members have failed to reveal consistent differences from the normal. Phenylpyruvic acid was not present in their urine,[3,28] nor was phenylalanine found in increased amounts in the blood.[55,106] The feeding of phenylalanine did not result in the excretion of phenylpyruvic acid,[27,28] although a more persistent elevation of plasma phenylalanine compared with that in normal controls was recently reported with phenylalanine tolerance tests.[93] Electroencephalographic tracings show no abnormalities.[6] Studies of blood groups have shown no evidence of genetic linkage.[6,8,25,32]

Biochemistry

A schematic diagram of the metabolic pathways of phenylalanine and tyrosine in the normal and in the phenylketonuric person is presented in the Figure. General reviews on the metabolism of these amino acids have been written by Lerner,[34] Knox,[35] and Dalgliesh.[104]

Under normal circumstances, as indicated by the solid black line in the Figure, a predominant pathway for the metabolism of phenylalanine is through tyrosine, which is then oxidized through numerous intermediate steps to acetoacetic and fumaric acids. In the phenylketonuric, represented by the broken line, there is an enzymatic defect involving hydroxylation of phenylalanine,[36] thus creating an excess of this amino acid in the body fluids and leading to its excretion in the urine together with its derivatives, phenylpyruvic, phenyllactic, and phenylacetic acids; the latter is conjugated with

Diagram of metabolic pathways in normal and phenylketonuric persons.
* This block, suggested by Boscott and Bickel (References 41 and 42), may not be related to an enzyme deficiency but rather to the high blood phenylalanine level. The pathway to the parahydroxyphenyllactic and parahydroxyphenylacetic acids is of minor quantitative importance in the phenylketonuric.



glutamine to form phenylacetylglutamine.[13,37,38] A small amount of phenylalanine is hydroxylated, however, to orthohydroxyphenylalanine (orthotyrosine), which then is metabolized through unknown intermediates to orthohydroxyphenylacetic acid; the latter is present in excess amounts in the urine.[39,40]

An additional defect involving the tyrosine derivatives is concerned with the partial failure to form 2,5-dihydroxyphenylpyruvic acid (not shown in diagram) from parahydroxyphenylpyruvic acid and has been suggested as the cause for the increased excretion of the parahydroxyphenyl acids, namely, parahydroxyphenylpyruvic, parahydroxyphenyllactic, and parahydroxyphenylacetic acids.[41,42] This probably represents a pathway of minor quantitative importance in the phenylketonuric. These derivatives are also found in the urine in increased amounts in prematurity, scurvy, and tyrosinosis, although different mechanisms may be involved in their production.

The location of the metabolic defect was first demonstrated by Jervis in a series of experiments in which it was found that the feeding of phenylalanine and tyrosine produced a rise in tyrosine-like substances in the sera of normal persons. In the phenylketonuric only tyrosine could produce the same effect, thus indicating a failure of conversion of phenylalanine to tyrosine.[43] Subsequent studies by Jervis[36] showed that whereas liver extract from normal patients catalyzed the conversion of phenylalanine to tyrosine in the presence of oxygen, phosphopyridine nucleotide, and nicotinamide similar extracts from two phenylketonuric persons failed to do so, suggesting a deficiency in a specific enzyme.

The enzyme has not been found in tissues other than the liver. This organ had been suggested as the site of the disturbance because of abnormal galactose tolerance tests and nonspecific fatty changes found on biopsy specimens.[6,44,45] Exsanguination studies had failed to demonstrate the presence of the enzyme in the blood.[46]

The hydroxylation of phenylalanine normally occurs at the para position (Figure). In the phenylketonuric, parahydroxylation is reduced about 90%,[47] orthohydroxylation is increased,[39,40] and metahydroxylation is absent.[42] The defect is apparently specific, since hydroxylation of other aromatic compounds, e. g., antipyrine, is not affected.[47] The suggestion has been made that the presence of increased amounts of ortho- and parahydroxylated compounds in the urine may result from a nonspecific hydroxylation of the phenylalanine derivatives.[48,49]

That derangements in tryptophane metabolism may occur in the phenylketonuric is suggested by the finding of increased amounts of indolelactic and indoleacetic acids in the urine.[50-52] Dent has commented on a relationship between some anomaly of tryptophane metabolism and the mental retardation found in these patients.[53] The psychotic behavior in some of these patients suggests the possibility of an abnormality in the formation or utilization of a tryptophane derivative, e. g., serotonin.

Abnormal amounts of phenylalanine and tyrosine derivatives in the body fluids represent the major biochemical abnormality in the phenylketonuric. A correlation between the quantity of phenyl compounds excreted and the degree of mental defect has been suggested[6,29] but has not been found by most authors.[55,57,63,166] Biochemical findings in the normal and in the phenylketonuric person are presented in Table 7. The serum of the phenylketonuric contains an increased amount of free phenylalanine, with fasting values from 15 to 60 mg. per 100 cc. compared with normal levels of approximately 1 mg. per 100 cc.[27,54,55,63]; the spinal fluid may contain 4-12 mg. per 100 cc.[54] and the sweat 8-10 mg. per 100 cc.[62] Studies of the amino acid composition of the body proteins show no significant difference from the normal,[58] although Schrappe[57] has found that the serum protein of the phenylketonuric contains increased amounts of phenylalanine.

Phenylalanine is present in increased quantities in the urine,[27,55,58,59,63] accounting in one study for 0.42% of the total urinary nitrogen as compared with 0.073% in the normal.[59] Increased excretion of other amino acids has been reported,[12,52] including a high taurine and sarcosine content [6] as well as an unidentified "nitrogen containing substance A."[60] Other than for the increased amount of phenylalanine, paper chromatograms of the urine on several of our patients showed a normal distribution of amino acids.

Small amounts (0.31-1.78 mg.) of phenylpyruvic acid are present in the plasma of the phenylketonuric.[61] Phenyllactic acid has not been found in the sera.[54] Jervis has recently mentioned finding phenylacetic acid in the blood.[5]

A gram or more of phenylpyruvic acid may be excreted in the urine daily.[1,27,58,62,63] Phenyllactic acid is present in smaller amounts.[13,59,63] Phenylacetic acid may be conjugated with glucuronic acid [5] or with glutamine to form phenylacetylglutamine,[13, 37,38] which in normal urine is present in amounts of 0.2-0.3 gm. per day, and in the phenylketonuric 2-3 gm. per day.[38] Acidification or bacterial action will hydrolyze the phenylacetylglutamine, liberating phenylacetic acid and producing the typical musty aromatic odor to the urine.

The ingestion by the phenylketonuric of a diet high in protein, phenylalanine, phenylpyruvic, or phenyllactic acids results in increased serum level of phenylalanine, as well as increased excretion of nonhydroxylated phenylalanine derivatives in the urine.[3,58,62,63] Plasma levels of phenylalanine may be dependent on the ability of the kidney tubule to reabsorb phenylalanine.[55] A protein-free diet will decrease the output of these compounds.[58] Glycine, alanine, valine, leucine, cystine, tryptophane, and glutamic acid have no effect.[3,62,63]

The lack of normal pigmentation in the phenylketonuric is thought to be related to the metabolic defect. Since phenylalanine is not hydroxylated to tyrosine, the precursor of melanin, a deficiency in tyrosine is presumed to be responsible for the failure of normal pigmentation. Dancis has presented evidence that high levels of phenylalanine may inhibit the conversion of tyrosine to melanin,[92] and when patients are placed on a low phenylalanine diet the inhibitory effect of the phenylalanine is removed and the hair begins to darken.[85,90] The feeding of additional tyrosine to phenylketonurics over a long period of time has also been reported to cause darkening of the hair.[6,65]

The administration of thiamin, nicotinamide, pyridoxine, citrovorum factor, ascorbic acid, thyroid extract, corticotropin (ACTH), and cortisone has had no effect on the clinical condition or the output of phenyl derivatives in the urine.[3,6,11,12,59,64] Large amounts of tyrosine fed over extended periods have caused only a darkening of the hair.[6,12,65] Glutamic acid has not altered the clinical picture.[12,13] L-glutamine has recently been reported to reduce the urinary excretion of phenylpyruvic acid.[66]

Few studies have been carried out on the serum proteins in phenylketonuria. Fractional precipitation with potassium phosphate showed a small increase in the globulin fraction.[73] Increased sedimentation rates have been reported [12] but were not confirmed by other authors or ourselves.[5] Tiselius electrophoretic patterns have shown changes in the beta-globulins of 8 of 17 patients.[74] These were commonest in younger children and disappeared when the patients were placed on low phenylalanine diets. Quantitative alterations in the serum proteins were not found. Paper and Tiselius electrophoretic patterns on three of our adult patients showed normal patterns. Studies on the chemical properties of hemoglobin in phenylketonuria are being carried out by Pauling.[75]

Creatinuria,[76] decreased cerebral utilization of oxygen,[77] normal thyroid activity, and normal levels of copper [100] cholesterol, calcium, phosphorus, and alkaline phosphatase have been reported.[6] Plasma

norepinephrine (Noradrenaline) and epinephrine (Adrenalin) levels are reported as slightly decreased below those of other mental defectives.[78]

Clinical Laboratory Studies

Plasma phenylalanine can be measured by nitration,[67,68] enzymatic conversion to the corresponding amine,[69] or microbiological assay.[70] There is no simple qualitative test to measure increased amounts in the sera, although paper chromatographic techniques are useful.[102]

Phenylpyruvic acid can be determined qualitatively by the addition of fresh 1%-10% ferric chloride solution to acidified urine. We have routinely used a 5% solution of $FeCl_3$ and acidified the urine with several drops of glacial acetic acid or later 0.1N HCl.[102] In the presence of phenylpyruvic acid an intense green or greenish-blue color develops immediately which gradually fades over an hour's time. In an infant suspected of having the disease, the test may be performed on the diaper. A positive reaction may not be expected during the first month. Therefore, early determinations of the serum phenylalanine are advisable.[105]

Normal urine shows a milky white precipitate with $FeCl_3$; the presence of diacetic acid is indicated by a reddish-brown color and salicylates by a purple reaction. A false positive reaction will occur if there are increased amounts of bilirubin in the urine.[5] When the bilirubin is removed by absorption with $CaCO_3$, the reaction becomes normal.

We have experienced some difficulty in obtaining consistently positive reactions to $FeCl_3$ in the urine of phenylketonurics. In two patients, after obtaining positive reactions, repeated urines on successive days were normal. Serum phenylalanine levels were 38 mg. per 100 cc. and 42 mg. per 100 cc.,[71] which confirmed the original diagnoses, and urine tests were positive on further examinations. Possible explanations for these normal reactions include the role of renal threshold on excretion or a temporary decrease in dietary intake of phenylalanine. The difficulty in obtaining consistently positive reactions suggests that a number of phenylketonurics may have been missed by failure of the urine to react to the $FeCl_3$ reagent on a single test.

It is advisable to carry out a second test by mixing equal amounts of urine and 2,4-dinitrophenylhydrazine in 1N HCl.* A positive test is indicated by the formation of a yellow turbidity within several minutes.[71] Although this test is reported to be more sensitive, the results in our laboratory have paralleled those using $FeCl_3$. Some confusion occasionally arises because of a faint precipitate already in normal urine. This reaction may be quantitated by alkalinization of the acid hydrazone.[58,72]

Electrocardiograms on our patients were normal and no evidence of a prolonged RST segment was found.[12]

Electroencephalographic studies of phenylketonurics have described normal patterns,[44] a slightly reduced alpha frequency,[79] low voltage and poor coordination between areas,[6,80] interseizure and seizure patterns,[6, 80,81] and discharges of the petit mal type.[80] Studies on our patients showed varying degrees of dysrhythmia and petit mal discharges. The degree of abnormality was not related to the severity of the mental defect, and several had normal patterns.†

Pathology

Pathological findings other than those in the central nervous system are not remarkable. Atrophy of the adrenals, pituitary, islands of Langerhans, and fibrous tissue of the liver has been reported.[12] No evidence exists that tyrosine deficiency causes dwarfing or pituitary degeneration, as suggested by Benda.[17]

* Reagent is prepared as follows: 1.4 gm. 2,4-dinitrophenylhydrazine is dissolved in 500 cc. 1N HCL by warming. Cool and store in a dark bottle.[71]

† Most of the patients had to be sedated, and on these only sleep records were available for interpretation. All recordings were made using an eight-channel Grass machine.

The most complete neuropathological studies are those of Alvord et al., who studied five cases.[82] The brains were small but without gross lesions. Microscopically there were defects in myelinization which appeared to be dependent upon the age of the patient and included the optic chiasm, corticospinal, corticopontocerebellar systems, auditory, olfactory, and peripheral nervous system. Benda studied two cases, both showing marked demyelinization, and implied that the disease was one of abnormal protein storage.[17]

Penrose[83] reported an interesting case of phenylketonuria in a 9-year-old boy who, at autopsy, showed nodular swellings along the vagus, celiac plexus, sciatic, and other nerves. Microscopic examinations suggested a diagnosis of neurofibromatosis. The tumors showed no reaction with ferric chloride; similar cases have not been reported.

Other authors have found evidence of mild cortical atrophy.[12] Corsellis likened the changes to those found in pellagra.[84] In one report no abnormal findings were noted,[18] and Jervis reported no changes in myelin formation in four of five cases.[5]

Treatment

Recent interest has centered on the treatment of phenylketonuria with a low phenylalanine diet. The first published report by Bickel and co-workers described a 2-year-old phenylketonuric who was fed a phenylalanine-free casein hydrolysate.[85] Physical improvement in terms of darkening of hair was noted in addition to some improvement in her mentality, general behavior, and attention span. The addition of 4 gm. of phenylalanine caused immediate regression in her behavior. Additional patients have been studied by these authors[86] and others from England[87] and the United States.[88-90]

The diets consisted of a casein hydrolysate with phenylalanine removed or a synthetic amino acid mixture supplemented with added carbohydrate, minerals, and vitamins. Improvement is first manifested biochemically. The plasma phenylalanine level drops rapidly to normal and the abnormal compounds disappear from the urine.

Clinically the children appear brighter, show an increased attention span, and manifest "mental development beyond that to be expected in untreated phenylketonurics."[86] Seizures, when present, have disappeared, and the EEG may return to a normal pattern. On return to a normal diet regression has been noted.

There is some variability in response, and not all observers have reported success.[53,88] Greater improvement may occur in children in whom treatment is started when they are less than 2 years old.[88] The longest period of treatment has been two and a half years. Horner and Streamer reported the treatment of a 7-week-old infant who for 1½ years has been developing normally.[89] This experience suggests the need to establish the diagnosis as early as possible. Siblings of known phenylketonurics should be repeatedly tested shortly after birth.

Comment

On clinical findings, it is difficult to identify the phenylketonurics. Although they are often described as mental defectives with blonde hair, blue eyes, fair skin, and dermatoses, this was not true of all patients in our series (Tables 2-4). Many of these signs also occur in nonphenylketonuric mental defectives. The diagnosis may be suspected by the strong musty or aromatic odor of the urine. The characteristic odor is found more frequently in the diapered or untidy child. It is not present, however, in all instances.

The urine of any child with mental deficiency, as well as that of a sibling of a phenylketonuric, should be tested several times for the presence of phenylpyruvic acid using both the ferric chloride and dinitrophenylhydrazine tests. Both tests can be easily performed in the office and will establish an accurate diagnosis in most cases. In some children a single normal test may be unreliable evidence to exclude phenylketonuria, and several urine speci-

mens should be examined. An unequivocal diagnosis may always be made by determination of the serum phenylalanine level, since this biochemical abnormality sharply separated the phenylketonuric from the non-phenylketonuric.[10,22]

Striking among these patients during childhood and later years is the psychotic behavior manifested by withdrawal from reality, failure to relate to people, absence of emotional responses (except for fright), the presence of echolalia, and stereotyped catatonic-like posturing. Although these findings may occasionally be seen in non-phenylketonuric defectives, their frequent occurrence among these patients calls attention to a possible correlation between biochemical abnormalities and mental aberrations.

Estimations of the prevalence of the disease suggest that a considerable number of phenylketonuric persons are unrecognized. Some of these may be among the less retarded, the psychotic, or the normal population. Surveys of these populations, using the $FeCl_3$ test, have revealed few instances of the disease, suggesting that phenylketonurics are more frequently found among the more severely retarded population.[15,26,91,100] Mass surveys so far may not have presented completely reliable evidence. The disorder occurs once in every 25,000 births; no survey has studied this number of persons. The $FeCl_3$ test may in some instances give false normal reactions. Phenylketonurics with normal or near-normal intelligence have been described,[5,6,9,26] and one of our patients (Case 21) has been released from the hospital and is making a satisfactory vocational adjustment in his community.

A more satisfactory approach would be through an intensive study of families for evidence of modified expressions of the disease, or evidence of the heterozygous state. Clinical or biochemical variability is slight among the reported persons with the disease. This is not consistent with the variability in clinical expression in other recessively inherited conditions, e. g., cystic fibrosis and sickle-cell anemia. That a phenylketonuric parent has given birth to an affected offspring[3,5,50] may suggest a different mode of inheritance, or the expression of this disease in other than the homozygous form.

The relationship between the mental defect and the biochemical findings has intrigued many investigators. No correlation has been found between the degree of mental defect and the concentration in the tissues or body fluids of the derivatives of phenylalanine and tyrosine.[6,13,29,42,55,57,61,62,63,99,106] Tyrosine deficiency has been suggested, although serum levels are normal and the feeding of added tyrosine has not altered the clinical picture.[6,63] Although phenylalanine serum levels are elevated, tissue concentrations so far have been found to be normal.[56]

It seems unlikely that damage to the fetus occurs in utero, since placental transfer would maintain the fetal phenylalanine levels at values close to normal. Biochemical observations on a newborn infant with phenylketonuria have recently been reported by Armstrong and Binkley and indicate that the biochemical changes take place after birth.[105] Further, gross congenital malformations or widespread microscopic changes suggesting prenatal injury have not been described in postmortem material. Damage to the nervous system may well occur during the first few years of life. Deterioration thereafter has not been demonstrated.

This observation is supported by results of treatment of phenylketonuric children with low phenylalanine diets.[85,99] Restriction of phenylalanine intake in the child under 2 years of age may result in greater clinical improvement than similar treatment in the older child[88]; a 1½-year-old phenylketonuric child has been maintained on a low phenylalanine intake since 7 weeks of age and has remained within normal developmental limits.[89] There is a possibility that low phenylalanine diets may not have

to be maintained after adequate development of the central nervous system is complete. A regular diet then may result in the occurrence of biochemical changes without the appearance of "delayed" mental retardation.[71]

The findings of indoleacetic and indolelactic acids in the urine of phenylketonurics may indicate derangements in the metabolism of tryptophane and the 5-hydroxylindole compounds.[95] Phenylalanine and tyrosine have also been suggested as possible precursors of 5-hydroxyindole compounds. The psychotic behavior of some phenylketonurics calls attention to the alleged role of these compounds, e. g., serotonin (5-hydroxytryptamine).[96] A reduction in the increased excretion of diazo-coupling compounds has been reported in the urine of schizophrenics when they are placed on a low phenylalanine-tyrosine diet.[97,98] The possible role of tryptophane abnormalities in the production of the mental defect and behavior of the phenylketonuric deserves further investigation.

Summary

A review of the literature on phenylketonuria and a report of 21 patients with this disorder are presented. The clinical picture, genetic features, biochemical abnormalities, pathology, and treatment are discussed.

Although there are frequent exceptions, the usual clinical findings include severe mental defect, blonde hair, blue eyes, fair skin, and dermatoses. Similar findings are present, however, in many nonphenylketonuric mental defectives. Attention is directed to the psychotic behavior in the phenylketonuric. The diagnosis is established by the finding of phenylpyruvic acid in the urine using the ferric chloride and dinitrophenylhydrazine tests.

The disease is transmitted as a simple Mendelian recessive; the frequency is estimated at 1 in 25,000 births. One in eighty persons is a carrier of the gene. Estimation of the prevalence suggests that a large number of phenylketonuric persons are unrecognized.

Biochemically, the disease is characterized by an enzymatic defect involving hydroxylation of phenylalanine to tyrosine. An excess of phenylalanine is found in the body fluids as well as excessive amounts of its phenyl derivatives in the urine.

Few pathological studies have been conducted, and no consistent changes have been noted by various observers.

Treatment with low phenylalanine diets has proved effective in reversing the profound biochemical changes. The ultimate benefit of these diets on the mental defect remains to be defined, although it is suggested that treatment at an early age may be effective in preventing a severe degree of mental defect.

Unexplained features of the disease include the following: the presence of psychological abnormalities associated with a metabolic defect; the relationship between the mental defect and the metabolic aberrations; the possible occurrence of the disease among the normal, the less retarded, and the psychotic population, and, finally, the role of tryptophane abnormalities in relation to the clinical manifestations of the disease.

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REFERENCES

1. Fölling, A.: Ueber Ausscheidung von Phenylbrenztraubensäure in den Harn als Stoffwechselanomalie in Verbindung mit Imbezillität, Ztschr. Physiol. Chem. 227:169, 1935.

2. Penrose, L. S.: Two Cases of Phenylpyruvic Amentia, Lancet 1:23, 1935.

3. Jervis, G. A.: Phenylpyruvic Oligophrenia: Introductory Study of 50 Cases of Mental Deficiency Associated with Excretion of Phenylpyruvic Acid, Arch. Neurol. & Psychiat. 38:944, 1937.

4. Brügger, C.: Die Ausscheidung von Phenylbrenztraubensäure im Urin von Schwachsinnigen, Schweiz. Arch. Neurol. u. Psychiat. 49:62, 1942.

5. Jervis, G. A.: Phenylpyruvic Oligophrenia (Phenylketonuria), A. Res. Nerv. & Ment. Dis., Proc. 33:259, 1954.

6. Cowie, V.: Phenylpyruvic Oligophrenia, J. Ment. Sc. 97:505, 1951.

7. Penrose, L. S.: Phenylketonuria: A Problem in Eugenics, Lancet 1:949, 1946.

8. Penrose, L. S.: Biology of Mental Defect, New York, Grune & Stratton, Inc., 1949.

9. Cowie, V. A.: Atypical Case of Phenylketonuria, Lancet 1:272, 1951.

10. Harris, H.: An Introduction to Human Biochemical Genetics, Eugenics Laboratory Memoirs, 37, London, Cambridge University Press, 1953.

11. Bates, R. M.: Three Cases of Phenylpyruvic Oligophrenia, J. Ment. Sc. 85:273, 1939.

12. Mautner, H., and Quinn, K. V.: Phenylpyruvic Oligophrenia, Ann. paediat. 172:1, 1949.

13. Woolf, L. I., and Vulliamy, D. G.: Phenylketonuria with a Study of Effect upon It of Glutamic Acid, Arch. Dis. Childhood 26:487, 1951.

14. Cowie, V. A., and Penrose, L. S.: Dilution of Hair Colour in Phenylketonuria, Ann. Eugenics 15:297, 1951.

15. Levy, S., and Perry, H. A.: Phenylpyruvic Acid Factor in Mental Deficiency and Mental Illness, Am. J. Ment. Deficiency 54:73, 1949.

16. Frazier, R. L.: Phenylpyruvic Amentia: Report of an Institution Survey, Am. J. Ment. Deficiency 51:577, 1947.

17. Benda, C. E.: Developmental Disorders of Mentation and Cerebral Palsies, New York, Grune & Stratton, Inc., 1952.

18. Josephy, H.: Phenylpyruvic Oligophrenia (Report on 16 Clinical Cases and 2 Autopsies), Illinois M. J. 94:107, 1948.

19. Cantor, S. J.: Phenylpyruvic Oligophrenia, with Notes on New Case and Report of Laboratory Investigations in an Earlier Case, M. J. Australia 1:69, 1952.

20. Warthen, R. O.; Tandeta, M., and Williams, J. M.: Phenylpyruvic Oligophrenia: 2 Cases of Siblings, Am. J. Dis. Child. 78:759, 1949.

21. Meldicott, R. W.: Phenylpyruvic Oligophrenia, New Zealand M. J. 43:101, 1944.

22. Penrose, L. S.: Measurement of Pleiotropic Effects on Phenylketonuria, Ann. Eugenics 16:134, 1951.

23. Penrose, L. S.: Inheritance of Phenylpyruvic Amentia (Phenylketonuria), Lancet 2:192, 1935.

24. Jervis, G. A.: Genetics of Phenylpyruvic Oligophrenia, J. Ment. Sc. 85:719, 1939.

25. Munro, T. A.: Phenylketonuria: Data on 47 British Families, Ann. Eugenics 14:60, 1949.

26. Larson, C. A.: An Estimate of the Frequency of Phenylketonuria in South Sweden, Folia hered. et path. 4:40, 1954.

27. Fölling, A., and Closs, K.: Über das Vorkommen von l-Phenylalanin in Harn und Blut bei Imbecillitas phenylpyrouvica, Ztschr. physiol. Chem. 254:115-116, 1938.

28. Brügger, C.: The Elimination of Phenylpyruvic Acid by Mentally Deficient Individuals, Schweiz. med. Wchnschr. 73:967, 1943; Abstract, J. Ment. Sc. 92:269, 1946.

29. Fölling, A.; Mohr, O. L., and Ruud, L.: Oligophrenia Phenylpyrouvica: A Recessive Syndrome in Man, Oslo, Dybwad, 1945.

30. Cohen, P., and Kozinn, P. J.: Phenylpyruvic Oligophrenia in Jewish Child, J. Pediat. 34:76, 1949.

31. Fernandes, J. F.: Phenylpyruvic Oligophrenia in the Dark-Skinned Person, Brasil-méd. 64:225, 1950; Abstract, J. Ment. Sc. 97:855, 1951.

32. Penrose, L. S.: A Search for Linkage Between the A. B. O. Agglutinogens and Phenylketonuria, Am. J. Ment. Deficiency 50:4, 1945.

33. Patients in Mental Institutions, Part 1, Public Institutions for Mental Defectives and Epileptics, U. S. Public Health Service Publication, No. 483, Part 1, 1952.

34. Lerner, A. B.: Metabolism of Phenylalanine and Tyrosine, in Advances in Enzymology, Edited by F. F. Nord, Vol. 14, New York, Interscience Publishers, Inc., 1953, p. 73.

35. Knox, W. E.: The Metabolism of Phenylalanine and Tyrosine, in Amino Acid Metabolism, Edited by W. D. McElroy and B. Glass, Baltimore, Johns Hopkins Press, 1955.

36. Jervis, G. A.: Phenylpyruvic Oligophrenia Deficiency of Phenylalanine-Oxidizing System, Proc. Soc. Exper. Biol. & Med. 82:514, 1953.

37. Woolf, L. I.: Excretion of Conjugated Phenylacetic Acid in Phenylketonuria, Biochem. J. 49:ix, 1951.

38. Stein, W. H., Paladini, A. C., Hirs, C. H. W., and Moore, S.: Phenylacetylglutamine as a Constituent of Normal Human Urines, J. Am. Chem. Soc. 76:2848, 1954.

39. Armstrong, M. D.; Shaw, K. N. F., and Robinson, K. S.: Studies on Phenylketonuria: II. The Excretion of o-Hydroxyphenylacetic Acid in Phenylketonuria, J. Biol. Chem. 213:797, 1955.

40. Armstrong, M. D., and Shaw, K. N. F.: Studies on Phenylketonuria: III. The Metabolism of o-Tyrosine, J. Biol. Chem. 213:805, 1955.

41. Boscott, R. J., and Bickel, H.: Detection of Some New Abnormal Metabolites in the Urine of Phenylketonuria, Scandinav. J. Clin. & Lab. Invest. 5:380, 1953.

42. Boscott, R. J., and Bickel, H.: Phenylalanine and Tyrosine Metabolism in Patients with Phenylketonuria, Biochem. J. 56:1, 1954.

43. Jervis, G. A.: Studies on Phenylpyruvic Oligophrenia: Position of Metabolic Error, J. Biol. Chem. 169:651, 1947.

44. Delay, J.; Pichot, P.; Delbarre, F., and Taseel, J.: L'oligophrénie phénylpyruvique; nouvelles observations, Bull. et mém. Soc. méd.

hóp. Paris 64:669, 1948. (Cited by Cowie, V. A.: J. Ment. Sc. 97:505, 1951.)

45. Cowie, V. A.: Galactose Tolerance Test in Phenylketonuria, J. Ment. Sc. 96:799, 1950.

46. Pichot, D.; Delay, J., and Bertagna, L.: L'oligophrénie phénylpyruvique, Extrait Annales Médico-Psychologiques, No. 3, 1949. (Cited by Cowie, V. A.: J. Ment. Sc. 97:505, 1951.)

47. Udenfriend, S., and Bessman, S. P.: Hydroxylation of Phenylalanine and Antipyrine in Phenylpyruvic Oligophrenia, J. Biol. Chem. 203: 961, 1953.

48. Weil-Malherbe, H., in Biochemistry of the Developing Nervous System, Edited by Waelsch, H., New York, Academic Press, Inc., 1955, p. 427.

49. Harley-Mason, J., and Cromartie, R. I. T.: Formation of Monohydroxyindoles from Dihydroxyphenalanine, Proceedings of the Biochemical Society, Biochem. J. 51:xxiv, 1952.

50. Armstrong, M. D., and Robinson, K. S.: On the Excretion of Indole Derivatives in Phenylketonuria, Arch. Biochem. 52:287, 1954.

51. Jepson, J. B.: Paper Chromatography of Urinary Indoles, Lancet 2:1009, 1955.

52. Ferrari, V.; Campagnari, F., and Guida, A.: Phenylpyruvic Oligophrenia: New Chemico-Pathological Findings, Minerva med. 46:119, 1955; Abstract, J. A. M. A. 159:1160, 1955.

53. Dent, C. E.: Personal Communication cited in Year Book of Pediatrics, 1955-56, Chicago, The Year Book Publishers, Inc., p. 59.

54. Jervis, G. A.; Block, R. J.; Bolling, D., and Kanze, E.: Chemical and Metabolic Studies on Phenylalanine: Phenylalanine Content of the Blood and Spinal Fluid in Phenylpyruvic Oligophrenia, J. Biol. Chem. 134:105, 1940.

55. Borek, E.; Brecher, A.; Jervis, G. A., and Waelsch, H.: Oligophrenia Phenylpyruvica; Constancy of Metabolic Error, Proc. Soc. Exper. Biol. & Med. 75:86, 1950.

56. Block, R. J.; Jervis, G. A.; Bolling, D., and Webb, M.: Chemical and Metabolic Studies on Phenylalanine: Amino Acid Content of Tissue Proteins of Normal and Phenylpyruvic Oligophrenic Individuals: Note on the Estimation of Phenylalanine, J. Biol. Chem. 134:567, 1940.

57. Schrappe, O.: Zur pathologischen Physiologie des Phenylbrenztraubensäure-Schwachsinns, Nervenarzt 23:175, 1952.

58. Penrose, L. S., and Quastel, J. H.: Metabolic Studies on Phenylketonuria, Biochem. J. 31:266, 1937.

59. Dann, M.; Marples, E., and Levine, S. Z.: Phenylpyruvic Oligophrenia: Report of Case in Infant with Quantitative Chemical Studies of Urine. J. Clin. Invest. 22:87, 1943.

60. Dobriner, K.; Rhoads, C. P., and Lieberman, S.: Spectroscopy as Applied to the Study of Phenylpyruvic Oligophrenia: Role of Nutritional Deficiency in Nervous and Mental Disease, Res. Nerv. & Ment. Dis. Proc. 22:158, 1943.

61. Jervis, G. A.: Studies on Phenylpyruvic Oligophrenia: Phenylpyruvic Acid Content of Blood, Proc. Soc. Exper. Biol. & Med. 81:715, 1953.

62. Jervis, G. A.: Metabolic Investigations on Case of Phenylpyruvic Oligophrenia, J. Biol. Chem. 126:305, 1938.

63. Jervis, G. A.: Excretion of Phenylalanine and Derivatives in Phenylpyruvic Oligophrenia, Proc. Soc. Exper. Biol. & Med. 75:83, 1950.

64. Lepow, H.: Phenylpyruvic Oligophrenia: A Clinical and Biochemical Study, Monatsschr. Psychiat. u. Neurol. 110:161, 1945; Abstract, J. Ment. Sc. 92:649, 1946.

65. Snyderman, S. E.; Norton, P., and Holt, L. E., Jr.: Effect of Tyrosine Administration in Phenylketonuria, Fed. Proc. 14:450, 1955.

66. Meister, A.; Udenfriend, S., and Bessman, S. P.: Diminished Phenylketonuria in Phenylpyruvic Oligophrenia After Administration of L-Glutamine, L-Glutamate or L-Asparagine, J. Clin. Invest. 35:619, 1956.

67. Albanese, A. A.: Colorimetric Estimation of Phenylalanine in Some Biological Products, J. Biol. Chem. 155:291, 1944.

68. Block, R. J., and Bolling, D.: Chemical and Metabolic Studies on Phenylalanine: The Nitration of Phenylalanine, J. Biol. Chem. 129:1, 1939.

69. Udenfriend, S., and Cooper, J. R.: Assay of L-Phenylalanine as Phenylethylamine After Enzymatic Decarboxylation; Application to Isotope Study, J. Biol. Chem. 203:953, 1953.

70. Prescott, B. A.; Borek, E.; Brecher, A., and Waelsch, H.: Studies on Oligophrenia Phenylpyruvica; Microbiological Determination of L- and D-Phenylalanine and of Phenyllactic Acid, J. Biol. Chem. 181:273, 1949.

71. Armstrong, M. D.: Personal communication to the authors.

72. Berry, J. P., and Woolf, L. I.: Estimation of Phenylpyruvic Acid, Nature, London 169:202, 1952.

73. Kondritzer, A. A.: Precipitation Pattern of Serum Proteins in Phenylpyruvic Oligophrenia, Proc. Soc. Exper. Biol. & Med. 44:404, 1940.

74. Brown, D. M.; Armstrong, M. D., and Smith, E. L.: Studies on Phenylketonuria: Serum Proteins in Phenylketonuria, Proc. Soc. Exper. Biol. & Med. 89:367, 1955.

75. Pauling, L.: Personal communication to the authors.

76. Pugh, C. E. M.: The Use of Creatine-Creatinine Ratio, J. Ment. Sc. 86:240, 1940.

77. Himwich, H. E., and Fazekas, J. F.: Cerebral Metabolism in Mongolian Idiocy and Phenyl-Pyruvic Oligophrenia, Arch. Neurol. & Psychiat. 44:1213, 1940.

78. Weil-Malherbe, H.: Blood Adrenalin and Intelligence, in Biochemistry of the Developing Nervous System, Edited by Waelsch, H., New York, Academic Press, Inc., 1955.

79. Kreezer, G. L.: Research in Progress upon the Electroencephalogram in Mental Deficiency. Proc. Am. Ment. Deficiency 63:120, 1939; Abstract, J. Ment. Deficiency 86:1123, 1940.

80. Fois, A.; Rosenberg, C., and Gibbs, F. A.: The Electroencephalogram in Phenylpyruvic Oligophrenia, Electroencephalog. & Clin. Neurophysiol. 7:569, 1955.

81. Gibbs, F. A., and Gibbs, E. L.: Phenylpyruvic Amentia, in Atlas of Electroencephalography, Reading, Mass., Addison-Wesley Publishing Company, Inc., 1950.

82. Alvord, E. C., Jr.; Stevenson, L. D.; Vogel, F. S., and Engle, R. L., Jr.: Neuropathological Findings in Phenyl-Pyruvic Oligophrenia (Phenylketonuria), J. Neuropath. & Exper. Neurol. 9:298, 1950.

83. Penrose, L. S.: Peripheral Nerve Tumors in Case of Phenylketonuria, Lancet 1:572, 1939.

84. Corsellis, J. A. N.: Pathological Report of Case of Phenylpyruvic Oligophrenia, J. Neurol. Neurosurg. & Psychiat. 16:139, 1953.

85. Bickel, H.; Gerrard, J., and Hickmans, E. M.: Influence of Phenylalanine Intake on Chemistry and Behavior of a Phenylketonuric Child, Acta. paediat. 43:64, 1954.

86. Bickel, H.; Boscott, R. J.; Gerrard, J., and Waelsch, H.: Observations on the Biochemical Error in Phenylketonuria and Its Dietary Control, in Biochemistry of the Developing Nervous System, Edited by H. Waelsch, New York, Academic Press, Inc., 1955.

87. Woolf, L. I.; Griffiths, R., and Moncrieff, A.: Treatment of Phenylketonuria with a Diet Low in Phenylalanine, Brit. M. J. 2:57, 1955.

88. Armstrong, M. D., and Tyler, F. H.: Studies on Phenylketonuria: Restricted Phenylalanine Intake in Phenylketonuria, J. Clin. Invest. 34:565, 1955.

89. Horner, F. A., and Streamer, C. W.: Effect of a Phenylalanine-Restricted Diet on Patients with Phenylketonuria, J. A. M. A. 161:1628, 1956.

90. Bosma, J. F.; Low, N. L.; Armstrong, M. D.; Tyler, F. H.; Madsen, J. A., and Carlisle, J. W.: Clinical Effects of Phenylalanine Restrictive Diet in Phenylketonuria, Presented at Society for Pediatric Research, Buck Hill Falls, Pa., 1956.

91. Cares, R. M.: Absence of Phenylketonuria in Adult Psychotics: A Survey of 4246 Inmates of a State Mental Hospital, Am. J. Psychiat. 112: 938, 1956.

92. Dancis, J., and Balis, M. E.: A Possible Mechanism for Disturbance in Tyrosine Metabolism in Phenylpyruvic Oligophrenia, Pediatrics 15:63, 1955.

93. Hsia, D. Y., and Driscoll, K.: Detection of the Heterozygote in Phenylketonuria, Presented at the Society for Pediatric Research, Buck Hill Falls, Pa., 1956.

94. Lorcomb, J. W.: Phenylketonuria and the Congenitally Deaf, J. Pediat. 14:348, 1939.

95. Udenfriend, S.; Titus, E.; Weissbach, H., and Peterson, R. E.: Biogenesis and Metabolism of 5-Hydroxyindole Compounds, J. Biol. Chem. 219:335, 1956.

96. Brodie, B. B.; Pletscher, A. B., and Shore, P. A.: Evidence that Serotonin Has a Role in Brain Function, Science 122:968, 1955.

97. McGeer, P. L.; McGeer, E. G., and Gibson, W. C.: Aromatic Excretory Pattern of Schizophrenics, Science 123:1029, 1956.

98. McGeer, P. L.; McGeer, E. G., and Boulding, J. E.: Relation of Aromatic Amino Acids to Excretory Pattern of Schizophrenics, Science 123:1078, 1956.

99. Boscott, J. R., in Biochemistry of the Developing Nervous System, Edited by H. Waelsch, New York, Academic Press, Inc., 1955, p. 428.

100. Larson, C. A.: The Absence of Phenylketonuria in 8220 Individuals not Known to be Mental Defectives, Novant'anni Delle Leggi Mendeliane, Rome, Instituto Gregorio Mendel, 1956, p. 311.

101. Crowe, F. W., and Schull, W. J.: Phenylketonuria: Studies in Pigment Formation, Folia hered. et path. 1:259, 1952.

102. Jervis, G. A.: Personal communication to the authors.

103. Horner, F. A., and Streamer, C. W.: Personal communication to the authors.

104. Dalgliesh, C. E.: Metabolism of the Aromatic Amino Acids, in Advances in Protein Chemistry, Vol. 10, New York, Academic Press, Inc., 1955.

105. Armstrong, M. D., and Binkley, E. L., Jr.: Studies on Phenylketonuria: V. Observations on a Newborn Infant with Phenylketonuria, to be published.

106. Waelsch, H.: Quantitative Aspects of the Metabolic Error in Oligophrenia Phenylpyruvica, in Biology of Mental Health and Disease, New York, Paul B. Hoeber, Inc., 1952.

107. Kobayashi, T.; Saito, T.; Kanamura, K., and Koga, F.: Ueber drei Geschwisterfälle der phenylpyruvischen Oligophrenie, Shonika Rinsko, 5:6, 1952.

108. Bhaskaran, K.: Phenyl Pyruvic Oligophrenia: A Short Review with the Report of an Affected Family, Indian M. Gaz. 87:506, 1952.

109. Cawte, J. E.: Phenylketonuria, M. J. Australia 2:15-19, 1954.

Recovery of Enteropathogenic Types of Escherichia Coli from Infants with Diarrhea

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Recent reports have demonstrated that the enteropathogenic serotypes of Escherichia coli (EPEC) are being found in increasingly large numbers of medical centers.[1-6] Furthermore, in those centers where a wider experience with new types has been gained, the importance of this group as etiologic agents is becoming more evident.[7-11] It is our impression that the EPEC are the commonest recognizable cause of infantile diarrhea. However, we also have seen instances where the EPEC were found in conjunction with Salmonella or Shigella.[1, 10,11] This aspect of the problem will be discussed below.

In September of 1955 attempts were made to determine whether or not EPEC were associated with diarrheal disease in infants and children admitted to the Los Angeles County General Hospital. As the study progressed it became apparent that the EPEC were being found at a fairly uniform rate from month to month resulting in an endemic situation in the young infant population, capable at any moment of reaching epidemic proportions in such highly susceptible groups as prematures and newborns.

Moreover, during the present study the limited value of sorbitol as a preliminary means of identification became apparent despite a previous report suggesting that the EPEC were slow fermenters of sorbitol and as such could be rapidly screened in stools cultured on sorbitol medium.[12]

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Material and Methods

Subjects.—A total of 256 infants were surveyed during the interval between September, 1955, and January, 1956. They represented all infants under 8 months of age admitted to both the Acute and Communicable Disease Units of the Los Angeles County General Hospital with a history and findings of acute diarrhea.

Methods.—In initiating this study it was necessary to impose some limitations on the manner in which stools were examined, since the personnel of the routine laboratory were being utilized. Consequently, it was felt that justification existed for relying on the use of sorbitol agar as a means of preliminary identification. Therefore, all stool specimens received in the laboratory were cultured on sorbitol agar, and any colonies not fermenting sorbitol within 24 to 48 hours were then placed on triple sugar agar, and those with fermentations characteristic of E. coli were then tested with the eight types of sera. Typing was done with specific OB antisera against the following serotypes of E. coli*: 0-26 B6, 0-55 B5, 0-86 B7, 0-111 B4, 0-119 B14, 0-125 B15, 0-126 B16, and 0-127 B8. Macroscopic slide agglutination with a 1:5 dilution of antiserum from each of the above types was carried out. The sera were prepared by inoculation of rabbits with viable organisms according to the technique described by Ferguson and Neter.[13] Positive tests were those having grossly visible ++++ agglutination. Occasionally clumping of ± to ++ was noted with some suspensions. These were interpreted as being negative reactions. This was decided when cross reactions between the eight types and their respective antisera were shown to occur but never more than ++. However, the homologous types gave sharp ++++ results. No attempt was made to define other antigenic groupings. In addition, the stools were routinely cultured on SS and other media for identification of other enteric organisms. Final

* Obtained from Dr. W. W. Ferguson, Michigan State Department of Health, Lansing, Mich.

TABLE 1.—*EPEC Diarrhea*

	Sept.	Oct.	Nov.	Dec.	Jan.	Total
Total cases surveyed	73	45	43	51	44	256
Cases positive for EPEC	16	13	20	10	15	74
Percentage positive	22%	29%	47%	20%	34%	29%
Number of deaths	2		1			

identification was done by use of type-specific antisera against the Shigella and Salmonella types.

Results

The total number of patients examined from September through January is shown in Table 1. The monthly percentage of infants with diarrhea from whom the EPEC were isolated ranged from 20% to 47%; the average being approximately 29% of all infants examined. These data include cases from the infant ward, the Communicable Disease Hospital, and one case from the premature nursery where infants born outside the hospital were housed. Table 1 also shows the infants with EPEC who died in September and November. These three infants were either terminal on admittance or were complicated by other serious illnesses.

Table 2 shows the monthly incidence of types of EPEC. The infants surveyed showed a total of 74 cases, and of this total 48 were due to the serotype 0-111 B4. All other types were found with the exception of serotype 0-127 B8. These data were modified by the use of sorbitol, for it is now clear that in utilizing the fermentation of sorbitol a certain number of cases will be missed. This was demonstrated when 25 specimens fermenting sorbitol showed 4 to be members of the EPEC group when tested with the eight types of antisera available. The sorbitol fermenters were two 0-26 B6 and two 0-55 B5.

The above data suggested that the EPEC may have been widespread in their distribution. However, when infants without diarrhea (from the same ward but in separate rooms from diarrhea cases) had their stools and immediate bedside environment examined for the presence of EPEC, none was found. Furthermore, in the case of the infant admitted from another hospital to the premature isolation ward, no evidence was found of an epidemic of diarrhea in the interval immediately preceding or following the admittance of this baby.

This was in contrast to the data on 65 of the infants (nine charts were not studied) with diarrhea who had EPEC in their stools, for 11 (17%) had a history of acquiring the disease in the hospital. One 2-month-old infant with congenital heart disease did not show any clear evidence of diarrhea and is included in this latter group. This infant represents the only case in the entire study where any question of the presence of diarrhea arose. This group had the same average age as those who acquired their infection outside the hospital. Furthermore, 16 babies (25%) had clinical recurrences of their diarrhea, a rate somewhat higher than has been reported before.

TABLE 2.—*Cases of Diarrhea Due to Enteropathogenic Coli, September, 1955-January, 1956*

Type	Sept.	Oct.	Nov.	Dec.	Jan.	Total
0-26	..	2	4	..	..	6
0-55	1	..	2	1	1	5
0-86	2	2	2	..	..	6
0-111	11	4	10	9	14	48
0-119	..	1	..	..	..	1
0-125	1	2	1	..	..	4
0-126	1	2	1	..	..	4
0-127	..	..	..	..	..	..
Total Positive	16(22%)	13 (29%)	20 (47%)	10 (20%)	15 (34%)	74

TABLE 3.—*Cases of Mixed Bacterial Diarrhea*

Case No.	Age	Days in Hosp.	Culture	Parenteral Fluids
1.	1 mo.	10	Shigella sonnei E. coli 0-86 B7	No
2.	3 mo.	7	Salmonella anatum E. coli 0-125 B15	No
3.	2 mo.	7	Salmonella oregon E. coli 0-125 B15	No
4.	5 mo.	13	Shigella boydii E. coli 0-111 B4	4 days
5.	7 yr.	9	Shigella flexneri E. coli 0-111 B4	2 days

The average age of this group was lowest suggesting that recurrences were commoner in the younger infants. It should be emphasized that these recurrences were not all bacteriologically proved cases but clinical relapses.

In Table 3 the five cases are shown in which combinations of EPEC with either Shigella or Salmonella were found. The age range of these cases is from 1 month through 5 months for four of the cases, and in one instance one 7-year-old girl was found to have two types (inadvertently this person had a stool examined because an error was made in listing the age on the laboratory slip). The length of stay in hospital was 7 days or more, although none was more than 14 days. Two of the cases were quite ill; the other three were not. The cultures in all cases showed the presence of the EPEC only on initial examination within 24 hours after admittance to the hospital. Subsequent cultures showed only the presence of the Shigella or Salmonella.

Comment

The experience gained with this group of cases strongly suggests that in this locale the EPEC agents are constantly present in the community and represent a smoldering situation in the age population investigated. Furthermore, in the data presented, an attempt to demonstrate the number of cases occurring as a result of being infected in the hospital showed approximately 17% of the cases in this group representing infections acquired in such a fashion. However, the remainder of them had the organism present on the initial stool examination obtained in the admitting room or shortly after admittance to the hospital. It seems that the bulk of these babies received their infections outside the hospital. Nevertheless, once the infection has penetrated the confines of the hospital a secondary focus is established from which further dissemination can be efficiently achieved. Other investigators have shown this to be true and emphasize the need for irradicating the hospital focus by mass antibiotic therapy. In this respect Wheeler [14] assumes all infants under 2 years of age with diarrhea are harboring large numbers of EPEC, and consequently should receive oral neomycin on admittance to the hospital. Once it has been established by stool culture that the EPEC are not present, therapy is discontinued. Such a plan effectively reduces the cases occurring as a result of hospital infection. In addition it should offer prompt, active therapy for those babies with diarrhea due to EPEC.

However, the problem of the infant who is an asymptomatic carrier, commonly by virtue of previous infection, still remains. The information available suggests that the disease is rarely seen in adults. Furthermore, the observations of Sears, Brownlee, and others [15-17] showed that "resident" strains of E. coli are present in the GI tract of adults for long periods of time, and feeding of other E. coli strains does not dislodge the "resident" strain. Changes in environment associated with vacations or town, and particularly periods spent in the hospital, appear to be most commonly asso- other intervals when time is spent out of ciated with change of "resident" strains. However, two infants studied by this group showed a more diversified pattern of E. coli

types in the stools. Furthermore, the length of time that strains remained as "residents" was considerably shorter than in the adults. These data reinforce the notion that the EPEC may have their major circulation in the younger aged members of the community. Under such circumstances the bulk of the disease can be assumed to be in the infant population. How much a part is played by the presence of "resident" strains remains to be seen. In this respect the presence of coproantibody may be an important factor. Nevertheless, the method of spread from family to family still remains an unanswered question.

The clinical types seen in our study varied from the severe explosive to mild, low-grade, persistent diarrhea. Intermediate types were combinations of the above. Some of the mild forms of the disease were diagnosed as feeding problems or gastrointestinal allergy and had frequent changes of feeding formulae.

The babies that were admitted to the hospital for some complaint other than the diarrhea which subsequently developed would occasionally become seriously ill with alarming rapidity. Furthermore, other infants would have a few loose stools persist for long periods of time and suddenly develop explosive diarrhea. One infant who died was discharged from the hospital after a mild episode and subsequently was readmitted with a severe explosive exacerbation.

The use of sorbitol agar as an aid in identifying the organisms results in data that represent a portion of the total cases. This is comparable to the variability of fermentations of sugars by other enteric organisms. Nevertheless, practical compromise often dictates the limits of a study. Under such circumstances information can be gained that is most helpful. The data indicate clearly that sorbitol, although useful as a screening device, has its limitations.

The pattern of disease seen in three of the five cases of double infections was that of nonspecific diarrhea. However, Cases 4 and 5 were much more suggestive of Shigellosis and point to the fact that the E. coli was not the major contributor to the disease picture. Furthermore, all the cases showed the Salmonella or Shigella organisms in the stool for several days longer than the E. coli types, again suggesting that the illness was largely the result of either the Salmonella or Shigella infection.

This problem of a dual infection deserves more attention. Under the circumstances the sum of disease-producing organisms may be large and result from other combinations of organisms than those listed above. We have had two infants with 0-111 B4 diarrhea who also had another untypable coli recovered from the blood. This was also the experience of Neter,[8] who reports an untypable E. coli recovered from the meninges of a child with meningitis and EPEC in his stool. Two infants who died also had Proteus morganii present in their stool specimens.

The tendency to grasp at the major pathogen and ignore the other organisms of dubious pathogenic potential could conceivably lead to critical situations. Under such circumstances it appears wiser to pay attention to the combined effects. It is tempting to speculate in situations where mixed infections occur regarding the role one or the other or the result of combinations might play in initiating the disease process. Moreover, the remote possibility, as has previously been suggested,[3] of a transduction of virulence by means of bacteriophage from one agent to the other also exists.[18,19]

Conclusions

During a five-month interval 256 babies with diarrhea were surveyed for the presence of enteropathogenic Escherichia coli in their stools and 74 cases were found. Sixty-five per cent of this group were due to serotype 0-111 B4 and the remainder were six other serotypes.

The rate of clinical relapse of diarrhea in the enteropathogenic E. coli was 25% and was observed more in the younger infants.

Seventeen per cent of the babies acquired their enteropathogenic E. coli infection in the hospital. The average age of these infants was the same as those who acquired their infection outside the hospital.

The endemic nature of the disease was demonstrated by the constant presence of the enteropathogenic E. coli. It is postulated that a primary endemic focus of infection is present in the infant population, a secondary epidemic focus is being seen as a result of hospital acquired infection.

Five cases of a combination of enteropathogenic E. coli and Shigella or Salmonella were also seen.

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REFERENCES

1. Stock, A. H., and Shuman, M. E.: Gastroenteritis in Infants Associated with Specific Serotypes of Escherichia Coli: I. Incidence of Specific Escherichia Coli Serotypes 0111:B4 and 055:B5 in the Pittsburg Area, Pediatrics 17:192, 1956.

2. Stock, A. H., and Shuman, M. E.: Gastroenteritis in Infants Associated with Specific Serotypes of Escherichia Coli: II. An Epidemic of Escherichia Coli 0111:B4 Gastroenteritis Involving Multiple Institutions, Pediatrics 17:196, 1956.

3. Neter, E.; Korns, R. F., and Trussell, R. E.: Association of Escherichia Coli Serogroup 0111 with 2 Hospital Outbreaks of Epidemic Diarrhea of the Newborn Infant in New York State During 1947, Pediatrics 12:377, 1953.

4. Stulberg, C. S.; Zuelzer, W. W., and Nolke, A. C.: An Epidemic of Diarrhea of the Newborn Caused by Escherichia Coli 0111:B4, Pediatrics 14:133, 1954.

5. Modica, R. I.; Ferguson, W. W., and Ducey, E. F.: Epidemic Infantile Diarrhea Associated with Escherichia Coli 111, B4, J. Lab. & Clin. Med. 39:122, 1952.

6. Wheeler, W. E., and Wainerman, B.: The Treatment and Prevention of Epidemic Infantile Diarrhea Due to E. Coli 0-111 by the Use of Chloramphenicol and Neomycin, Pediatrics 14:357, 1954.

7. Jameson, J. E.; Mann, T. P., and Rothfield, N. J.: Hospital Gastro-Enteritis: An Epidemiological Survey of Infantile Diarrhea and Vomiting Contracted in a Children's Hospital, Lancet 2:459, 1954.

8. Neter, E.; Webb, C. R.; Shumway, C. N., and Murdock, M. R.: Study on Etiology, Epidemiology, and Antibiotic Therapy of Infantile Diarrhea, with Particular Reference to Certain Serotypes of Escherichia Coli, Am. J. Pub. Health 41:1490, 1951.

9. Taylor, J., and Charter, R. E.: Isolation of Serological Types of Bact. Coli in 2 Residential Nurseries and Their Relation to Infantile Gastroenteritis, J. Path. & Bact. 64:715, 1952.

10. Cooper, M. L.; Walters, E. W., and Keller, H. M.: Detection of a New Serotype of Escherichia Coli, E. Coli 0127:B8, Associated with Acute Diarrhea in Infants, J. Bact. 69:689, 1955.

11. Ewing, W. H.; Galton, M. M., and Tanner, K. E.: Escherichia Coli 0111a, 111c:B4: A New Serotype Isolated from Monkeys, J. Bact. 69:549, 1955.

12. Quilligan, J. J., Jr.: A Pathogenic Type of E. Coli (0-111 B4) in Infantile Diarrhea, A. M. A. Am. J. Dis. Child. 89:696, 1955.

13. Ferguson, W., and Neter, E.: Examinations for Enteropathogenic Escherichia Coli: "Diagnostic Procedures and Reagents," Am. Public Health Association, New York, to be published.

14. Wheeler, W. W.: Spread and Control of E. Coli Diarrheal Disease, Academy of New York Science, Ann. New York Acad. Sc. 66:112, 1956.

15. Sears, H. J.; Brownlee, I., and Uchiyama, J. K.: Persistence of Individual Strains of Escherichia Coli in the Intestinal Tract of Man, J. Bact. 59:293, 1950.

16. Sears, H. J., and Brownlee, I.: Further Observations on the Persistence of Individual Strains of Escherichia Coli in the Intestinal Tract of Man, J. Bact. 63:47, 1952.

17. Sears, H. L.; Janes, H.; Saloum, R., Brownlee, I., and Lamoreaux, L. F.: Persistence of Individual Strains of Escherichia Coli in Man and Dog Under Varying Conditions, J. Bact. 71:370, 1956.

18. Lederberg, J.; Lederberg, E. N.; Zinder, N. D., and Lively, E. R.: Recombination Analysis of Bacterial Heredity, Cold Spring Harbor Symposia Quant. Biol. 16:413, 1951.

19. Zinder, N. D., and Lederberg, J.: Genetic Exchange in Salmonella, J. Bact. 64:679, 1952.

Metharbital (Gemonil) in Myoclonic Spasms of Infancy and Related Disorders

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Six years have elapsed since a previous report [1] was published on the uses of metharbital (Gemonil) (5,5-diethyl-1-methylbarbituric acid) in various convulsive disorders. This relatively new, nontoxic barbiturate, which had shown marked anticonvulsant activity against pentamethylenetetrazol (Metrazol)-induced convlusions in mice and cats,[2] was found to be clinically effective in dosages which did not produce sedation.

Since no single drug is effective in all types of seizures, and since certain drugs have selective beneficial effects in specific types of seizures, it is always worth while subjecting new drugs to a critical evaluation. In the previous clinical investigation of metharbital (at that time known as Gemonal) 50 patients were studied, ranging in age from 4 months to 64 years. The average age was about 8 years, and dosage varied from 20 mg. to 180 mg. (⅓ to 3 grains) given two to four times daily, according to the patient's requirements. Metharbital was supplied in the form of a 100 mg. (1½ grains) scored tablet.

In this early study it was noted that metharbital had less soporific effect than either phenobarbital or mephobarbital (Mebaral), and this observation explains why the drug has been recommended and widely used as a mild daytime sedative. No blood changes were detected in any of the patients during a three-year period of observation, and the only evidence of toxic reaction was a transient morbilliform rash which developed in one patient. Metharbital benefited 18 of 35 patients with seizures due to organic brain disease but virtually failed to produce any beneficial response in patients with idiopathic epilepsy or with cerebral palsy. A notable feature was the rather consistent improvement seen in patients with myoclonic spasms of infancy.

At the conclusion of this earlier investigation it was felt that metharbital was a valuable drug in the treatment of epilepsy. It appeared to have the unique property of greater effectiveness in the organic rather than the idiopathic form of the disease. As a result of its promising features, the study of the effectiveness of metharbital was continued and is brought up to date in this present report.

Present Investigation

This report includes the results from the 50 patients studied previously, together with a further 150 cases. In this total of 200 patients there were 44 with multiple diagnoses (4 with three diagnoses each) so that a total of 248 diagnostic categories is available for analysis.

The ages of the patients ranged from 2 months to 64 years, with an average of approximately 7 years. There were 122 males and 78 females; 33 were Negroes, the remainder white. There was no demonstrable relationship between clinical results and sex or race.

The dosage of metharbital varied from 15 mg. to 180 mg. (¼ to 3 grains) two to four times daily. In general the dosage was gradually increased until either improvement or drowsiness oc-

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The metharbital (Gemonil) was supplied by Dr. R. K. Richards, of Abbott Laboratories.

TABLE 1.—*Effect Metharbital by Diagnostic Category*
(248 Diagnoses)

		Total Number (N) (100%)	Degree of Benefit							
			Marked		Moderate		No Benefit		Aggravated	
			N	%	N	%	N	%	N	%
Total series		248	41	17	28	11	170	68	9	4
Diagnostic Group	Total epileptic	203	41	20	26	13	127	63	9	4
	Total nonepileptic	45	0	0	2	5	43	95	0	0
	Cerebral palsy	33	0	0	1	3	32	97	0	0
	Athetoid	17	0	0	0	0	17	100	0	0
	Spastic	12	0	0	1	8	11	92	0	0
	Rigidity and tremor	4	0	0	0	0	4	100	0	0
	Behavioral and emotional	12	0	0	1	8	11	92	0	0

curred. It was found of no benefit to increase the dosage beyond the point of drowsiness or in any event beyond 180 mg. (3 grains), since added clinical improvement did not occur.

Results

The results of treatment were divided into four categories:

1. *Marked Improvement.*—Patients in this group were judged to show more than 75% benefit. This impression was based on a diary kept by the parents of the patient, indicating the frequency and severity of the seizures, and upon the clinical judgment of the examiner. In most instances the improvement within this category was both immediate and total.

2. *Moderate Improvement.*—The criteria for assessing the results were the same, and patients judged to show between 50% and 75% benefit were placed in this group.

3. *No Improvement.*—All patients showing less than 50% benefit from treatment were placed in this group. Also, in keeping with the principle that therapeutic effects must precede toxic effects in an anticonvulsant drug,[3] all patients in whom drowsiness or dizziness occurred before improvement was evident were placed in Group 3.

Similarly, patients who reacted as well to a placebo as to metharbital were classed as "not improved."

4. *Aggravated.*—Patients were placed in this group when the frequency or severity of the seizures was increased.

Analysis of Results

From Table 1 it is seen that of the 248 diagnostic entities available for study metharbital was of benefit in only 28% (17% marked benefit, 11% moderate benefit).

However, when the cases are divided into an "epileptic" group of 203, and a "nonepileptic" group of 45, it is evident that metharbital was of practically no value in promoting relaxation in 33 patients with cerebral palsy, or in improving behavioral disturbances in 12 children.

In the 203 instances of epilepsy the drug was of benefit in 33% (20% marked improvement and 13% moderate improvement). All these cases had proved resistant to other drugs, and it should be noted that our criteria for improvement were unusually strict.

When the epileptic group is broken down further, according to the types of seizure (Table 2), it becomes apparent that metharbital was most effective in the myoclonic spasms of infancy (66% of 54 cases).

It is of additional interest that in nine cases of infantile myoclonic spasms, in which there coexisted another variety of epileptic seizure (seven of which were grand mal), metharbital had a selective effect on the myoclonic seizures only. It produced marked benefit in eight of these children and moderate benefit in one, with regard to control of the myoclonic seizures; but in none of these cases did it exert any influence on the other types of seizures present. This

TABLE 2.—*Effect of Metharbital by Seizure Type*

	Total Number (N) (100%)	Degree of Benefit							
		Marked		Moderate		No Benefit		Aggravated	
		N	%	N	%	N	%	N	%
Total	203	41	20	26	13	127	63	9	4
Grand mal	73	5	7	11	15	55	75	2	3
Petit mal	43	3	7	6	14	28	65	6	14
Psychomotor	5	0	0	0	0	5	100	0	0
Myoclonic	54	30	55	6	11	17	32	1	2
Focal and Jacksonian	19	3	15	3	15	13	70	0	0
Vegetative and other	9	0	0	0	0	9	100	0	0

observation adds considerably to the impression that metharbital has a selective action in controlling myoclonic seizures.

Metharbital was of value in the treatment of focal and Jacksonian spells (30% of 19 cases). It was of occasional value in the treatment of grand mal (22% of 73 cases) and also in petit mal (21% of 43 cases). It was of no value in five cases of psychomotor epilepsy and nine cases of vegetative and related types of seizure.

In considering these figures it must be kept in mind that most of the patients in this series were severely involved and had proved "resistant" to other forms of drug therapy. The benefit reported was brought about either by the use of metharbital alone or by adding metharbital to a previously stabilized regimen. Also, the percentages obtained in this study (with regard to improvement) may differ from those that would be found in a general cross section of epileptics, since special circumstances made this series "overweighted" with cases of infantile myoclonic spasms and other types of epilepsy associated with organic disease of the brain.

It is a general observation that seizures due to organic brain disease are more resistant to drug therapy than the so-called "idiopathic" types of epilepsy; yet, when the epileptics are divided into those associated with organic disease of the brain and those classed as "idiopathic," it is seen that metharbital is much more effective in the group with epilepsy due to organic disease (Table 3).

Of the total epileptic cases, 41% of 155 benefited in the groups with seizures due to organic disease, as compared with only 6% (of 48) of the "idiopathic" cases. Likewise, in the grand mal group there was benefit in 28% (of 53) of "organic" cases, and only in 5% (of 20) of the "idiopathic." Similarly, in the petit mal group the figures are 35% benefited (of 20) with organic brain disease and only 9% benefited (of 23) "idiopathic" cases.

Of the total epileptic group of 203, only 9 were made worse by metharbital. Again, it

TABLE 3.—*Effect of Metharbital on "Organic" vs. "Idiopathic" Seizures*
(Total Number, 203 Cases)

		Total Number (N) (100%)		Degree of Benefit							
				Marked		Moderate		No Benefit		Aggravated	
				N	%	N	%	N	%	N	%
Total	Organic Brain Disease	155		41	26	23	15	87	56	4	3
	"Idiopathic"	48		0	0	3	6	40	83	5	11
Grand Mal	Organic brain disease	53	73	5	9	10	19	37	70	1	2
	"Idiopathic"	20		0	0	1	5	18	90	1	5
Petit Mal	Organic Brain Disease	20	43	3	15	4	20	11	55	2	10
	"Idiopathic"	23		0	0	2	9	17	73	4	18

is interesting to note that metharbital is less harmful in epileptics with organic brain disease, since only 4 of 160 (2½%) "organic" epileptics had their symptoms aggravated, as compared with 5 of 43 (12%) of the "idiopathic" cases.

Toxic Effects

Metharbital was singularly free of toxic side-effects. There were no cases in which the blood, urine, or liver profiles were abnormal. The commonest side-effect was somnolence, usually seen only when large doses were given and often associated with and unsteady or drunken gait. As with other barbiturates, an occasional patient seemed to be particularly sensitive to the drug; others were able to take large doses (up to 290 mg. [4½ grains]) without any soporic effect. A skin rash (morbilliform in nature) occured in only two cases. In both, the rash first appeared about 12 days after treatment was commenced and disappeared within 48 hours of stopping the drug. In both cases also, the rash was reproducible by giving the drug again.

It was unfortunate that both these cases of skin sensitivity occurred in patients who were markedly benefited by the drug, and in one of the patients, a 6-year-old girl, even small doses (24 mg. [⅜ grain]) caused sleepiness and an unsteady gait.

Comment

It is first necessary to clarify our diagnostic criteria when we speak of "myoclonic seizures" or "myoclonic spasms of infancy," since some confusion has existed in the use of this terminology in the literature, the terms "lightning grand mal" and "myoclonic petit mal" and many other names being used synonomously.

In the present report this diagnosis is applied only to the following type of seizure. It is a sudden, generalized spasm involving principally the arms, legs, and head, which resembles a "startle reflex." It occurs with lightening rapidity and is only momentary, rarely lasting a second. Often, there are cycles of repeated spasms, from 3 to 10 in a series of short intervals, interspersed with longer intervals of freedom. Less frequently the spasms are single. The frequency may vary from a few to several hundred daily. The condition occurs in infancy, usually after the sixth month, and is rarely seen after the third year. It is usually associated with organic brain disease and carries a poor prognosis for intellectual and physical normality. The electroencephalogram usually discloses a hypsarrhythmia.[4] It should be noted particularly that this diagnosis is not applied to the type of spasm which persists for from one to five seconds or longer or to spasms which are focal in nature. To satisfy our criteria the spasms must be both generalized and momentary.

Since myoclonic spasms of infancy are generally resistant to drug therapy, it is especially gratifying to find that metharbital exerts a favorable, selective action in this condition. Usually, if metharbital is effective, this becomes apparent within 24 to 48 hours of commencing treatment, and in our experience it is the most effective drug for the treatment of this type of seizure.

The specific effect of metharbital on infantile myoclonic spasms is confirmed by the results in cases in which grand mal, petit mal, and vegetative seizures occurred also. Usually these latter conditions are unimproved, although the myoclonic spasms respond favorably. To control the other epileptic manifestations it is usually necessary to prescribe additional anticonvulsant drugs, such as diphenylhydantoin (Dilantin) sodium or phenobarbital, and it is found that these additions do not interfere in any way with the actions of metharbital in controlling the myoclonic spasms.

It should be noted that even in cases in which metharbital controls the myoclonic spasms there is not necessarily a return of the electroencephalographic pattern to normal. In this respect metharbital resembles diphenlhydantoin, which may control grand mal seizures adequately without producing

any change in the EEG findings. By contrast the control of petit mal by trimethadione (Tridione) is often associated with a rapid return of the EEG pattern to normal. However, we have observed that when control of myoclonic spasms with metharbital has been maintained for several weeks or months there is a tendency for the electroencephalogram to improve or eventually to normalize.

In instances in which metharbital produces a favorable response, discontinuing the drug is frequently followed by a recurrence of the seizures, though this does not invariably occur. Status epilepticus has not been observed during the course of this investigation when metharbital was discontinued.

Summary

An expanded study of the therapeutic effect of metharbital (Gemonil), a relatively nontoxic barbiturate, is reported. 200 patients, aged 2 months to 64 years, and embracing 248 clinical entities were studied.

Metharbital was found to be of practically no value in reducing the spasticity or tensions of patients with cerebral palsy or in improving behavior or emotional disturbances.

The drug had the unique property of being approximately seven times more effective in seizures associated with organic brain disease (41%) than in the idiopathic forms of epilepsy (6%).

Metharbital was found to be most effective in controlling myoclonic spasms of infancy, more so than any other drug. It benefited 66% of the patients, in whom this diagnosis was made according to criteria discussed.

The drug was also found to benefit some patients with focal and Jacksonian spells (30%) and to a lesser extent grand mal (22%) and petit mal seizures (21%).

The drug is practically nontoxic. Its soporific effect is less than one-half that of phenobarbital—only two instances of rashes and no other side-effects were observed.

Metharbital is a valuable adjuvant in certain forms of epilepsy due to organic brain disease and particularly in the myoclonic spasms of infancy.

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REFERENCES

1. Perlstein, M. A.: Gemonal (5,5-Diethyl 1-Methyl Barbituric Acid), New Drug for Convulsive and Related Disorders, Pediatrics 5:448, (March) 1950.

2. Everett, G. M., and Richards, R. K.: Anticonvulsant Action of Drugs Against Metrazol and Antiepileptic Activity, Fed. Proc. 5:26 (Feb.) 1946.

3. Perlstein, M. A.: Symposium on Efficacy of New Drugs: The Drug Therapy of Epilepsy with Special Reference to Newer Drugs, Med. Clin. North America 38:473 (March) 1954.

4. Gibbs, E. L.; Fleming, M. M., and Gibbs, F. A.: Diagnoses and Prognosis of Hypsarhythmia and Infantile Spasms, Pediatrics 13:66 (Jan.) 1954.

Chronic Constrictive Pericarditis in Children

Report of a Case and Observations in Seven Others

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Chronic constrictive pericarditis is diagnosed far less frequently in children than in adults and is particularly rare before the age of 10 years. Because the disease is so seldom encountered in pediatric practice and often presents a clinical picture seemingly unrelated to the heart and its coverings, it often poses a problem in diagnosis. On the other hand, when this entity is considered as a possible underlying cause of relatively symptomless hepatomegaly and ascites and appropriate laboratory studies are carried out the presence of the condition may be demonstrated and optimal results may be obtained from operation.

A case of constrictive pericarditis recently encountered in an 8-year-old child illustrates not only some of the clinical features of the disease and pitfalls in diagnosis but also the value of certain laboratory procedures and effects of surgical correction. A report of this case follows, and the findings in seven other cases in children encountered at the Mayo Clinic in the past 25 years are reviewed.

Report of a Case

An 8-year-old white boy was brought to the Clinic on May 31, 1955, on referral by his private physician because of persistent enlargement of the liver, known to have been present for 4 months.

The family history was noncontributory. The past history revealed that he was a term infant and that his mother's pregnancy, labor, and delivery had been normal. Growth and development were not unusual, and the child had been considered to be in good health. He had had a mild diarrhea at the age of 18 months, bronchial pneumonia at the age of 2 years, and measles, mumps, and chickenpox before the age of 5. In early childhood he had been troubled with recurring bouts of tonsillitis until tonsillectomy and adenoidectomy were performed at 3 years of age. At no time had there occurred illnesses suggestive of either rheumatic fever or tuberculosis.

The time of onset of the present illness could not be definitely ascertained. His mother had been concerned about his unusually large abdomen for at least two years. This, together with a feeling of abdominal fullness experienced by the youngster, prompted his mother to seek medical attention. When examined by his private physician in February, 1955, the patient was found to have abdominal distention, marked enlargement of the liver, and ascites. He entered the local hospital for further evaluation, at which time mild anemia was found.

The boy returned to school shortly thereafter. From February until May, 1955, he remained symptomless and, except for abdominal fullness, his physical condition remained unchanged.

Because of the persistent hepatomegaly and ascites, exploratory laparotomy was performed and a greatly enlarged and engorged liver was found, together with free fluid in the peritoneal cavity. The spleen and mesentery were described as normal. Wedge biopsy of the liver revealed chronic passive congestion. The patient was referred to the Mayo Clinic for further evaluation.

Physical examination on May 31, 1955, revealed a well-developed, well-nourished, 8-year-old white boy who was in no distress. His height was 52½ in. and his weight was 62 lb. The pulse rate was 88 beats per minute and the respiratory rate was 20. The blood pressure varied from 110 mm. of mercury systolic and 70 mm. diastolic to 86 systolic and 60 diastolic. When the child was standing, the abdomen appeared enlarged, particularly in the upper quadrants, with bilateral spreading of the lower part of the thoracic cage. There was a well-healed, 2-in. vertical incisional scar in the right upper quadrant. Many prominent superficial veins were present over the abdomen but none was dis-

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Fig. 1.—Roentgenogram illustrating normal cardiac size and normal pulmonary vascular shadows.

tended. In the supine position, the superficial veins of the neck appeared distended but did not pulsate. The distention disappeared when the child assumed the semisitting position. The heart sounds were considered normal by most examiners, but one described a "ticktock" quality of little vigor. The liver was enlarged to 3 in. below the right costal margin and was firm and smooth and had a distinct edge. There was shifting dullness on percussion of the abdomen. The remainder of the physical examination gave negative results.

The results of blood studies on admission were within normal limits. Urinalysis disclosed grade 1 albuminuria, grade 1 erythrocyturia, and grade 1 leukocyturia. This examination was repeated with similar results. The prothrombin time was 24 seconds (normal 19 seconds). The results of tuberculin tests with first-strength and second-strength PPD (purified protein derivative) were negative after 48 hours. Initial x-ray examination of the thorax (Fig. 1) was interpreted as giving negative results. A plain roentgenogram of the abdomen showed haziness over the upper part of the abdomen with probable hepatomegaly.

The electrocardiogram (Fig. 2) might well have been considered as indicative of normal conditions except that the ventricular complexes in both standard and thoracic leads were of low amplitude for a child of this age and body build. In addition, the T-waves in S_1, S_3, and in V_4 were of low amplitude. Venous pressure obtained in the left antecubital vein at atrial level was found to be elevated to 15.0 cm. of water. Fluoroscopic examination of the heart indicated that cardiac pulsation was not very vigorous. No calcification was seen. Constrictive pericarditis was believed present by the fluoroscopist.

Cardiac catherterization was performed on June 17, 1955 (Table 1). Mean pressures in the great veins and right atrium were found to be significantly elevated. Right ventricular and pulmonary arterial systolic pressures were slightly greater than normal, and right ventricular diastolic pressure was significantly elevated. Pulmonary-artery-wedge pressure was also moderately elevated. There was

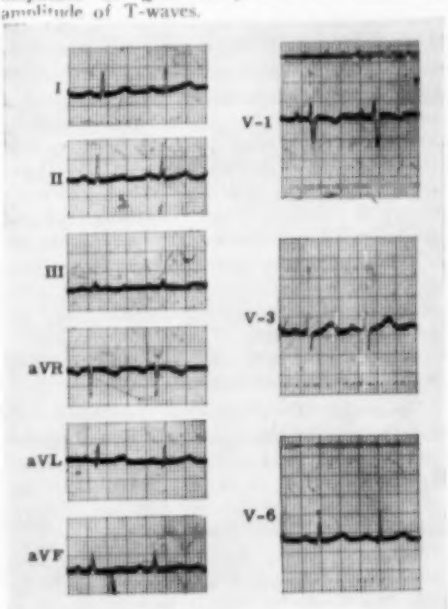
TABLE 1.—*Summary of Cardiac Catheterization Data from an Eight-Year-Old Child*

Breathing Air	Pressure, Mm. of Mercury	
	Found	Normal
Brachial vein	15	
Inferior vena cava	14	4 to 13
Mid right atrium	15	2 to 10
Right ventricle	33/18	23/3
Pulmonary artery	31/23	22/12
Pulmonary artery wedge	23/16	15/9
Radial artery	91/60	

Cardiac output: 4.4 liters per minute per square meter of body surface with air being breathed (normal 2.5 to 5.3)

a definite "square root" pattern in the diastolic period of the right ventricular pressure recording (Fig. 3), indicative of an impedance to diastolic filling. Mixed venous systemic saturation was within the range of normal. A selective angiogram accomplished by injection of 70% solution of sodium acetrizoate (Urokon Sodium) low in the right ventricle was suggestive of an abnormal right ventricular silhouette in the anteroposterior pro-

Fig. 2.—Electrocardiogram demonstrating low amplitude of QRS complexes and diminished amplitude of T-waves.



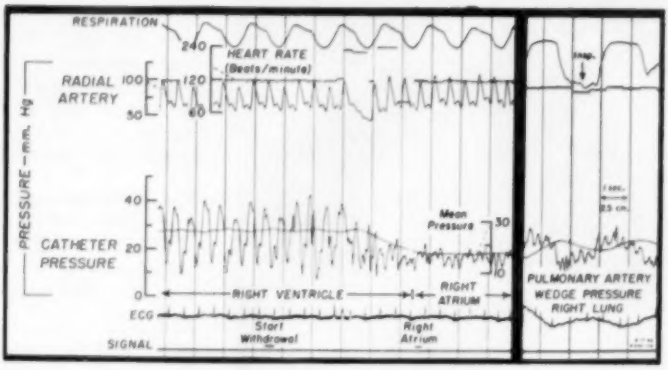


Fig. 3.—Reproduction of actual recording made during cardiac catheterization. The right ventricular systolic pressure is slightly elevated, but the early diastolic pressure is definitely above normal, and the end diastolic pressure is significantly increased, producing the configuration referred to as the "square root sign" which reflects the inability of the ventricle to distend normally during diastolic filling. The mean right atrial and pulmonary arterial wedge pressures are also higher than normal.

jection. As the catheter passed into the pulmonary artery its course was deviated toward the right more than usual. The findings were considered compatible with the presence of a mass in part of the right ventricular cavity.

With the previous clinical, electrocardiographic, fluoroscopic, and cardiac-catheterization findings supporting a diagnosis of constrictive pericarditis, but with angiocardiographic findings compatible with the presence of an intracardiac mass, exploratory thoracotomy was decided upon.

At operation both lungs were found slightly adherent to the pericardium. The pericaridum was thick, and as it was incised it was evident that this tissue acted as a constricting peel about both atria and ventricles, although it was not adherent to the surface of the heart. The pericardium was removed by sharp dissection from the entire right and left ventricular surfaces and from a portion of the right atrium, thus completely decorticating both ventricles. The right ventricle was carefully palpated, and no suggestion of intraventricular mass was detected. It was noted during the procedure that constriction of the right ventricle was greater than that of the left and that the right ventricular cavity was the smaller of the two before decortication. The gross specimen of pericardium measured 9 by 7 cm. and was 3 mm. thick. The microscopic appearance was that of pericarditis with increased vascularity and fibrinous exudate.

The postoperative course was complicated early by rather persistent tachypnea and respiratory distress, abdominal distention, and increased ascites. He was digitalized on the first postoperative day and maintained thereafter on digitoxin. He was dismissed on the ninth postoperative day.

Cultures from the pericardium, including those for Brucella and fungi, were reported as negative. The results of cultures and guinea pig inoculation for tuberculosis were reported as negative after six weeks.

Evaluation by the referring physician * one year after operation revealed no evidence of ascites although the liver was still palpable. The administration of digitoxin had been discontinued.

Summary of Data in Eight Cases

During the period 1930 through 1955, constrictive pericarditis was diagnosed at the Mayo Clinic in eight patients less than 15 years of age. The diagnosis was proved at operation or necropsy. Four of these cases were previously reported by Harrington [2] in a paper devoted primarily to surgical treatment, and one of the four was reported by Leaman and Vastine [4] in an article which dealt essentially with radiologic aspects. The clinical features of these eight cases are summarized in Table 2, the electrocardiographic, x-ray, and laboratory features in Table 3, and results of treatment in Table 4.

Comment

Constrictive pericarditis is a condition resulting from fibrotic thickening and contracture of the pericardium, with or without calcification. These changes cause interference with ventricular diastolic filling and to a lesser extent systolic emptying and pro-

* Dr. John McGregor, of the McGregor Clinic, Great Falls, Mont., referred the patient and evaluated his condition postoperatively.

TABLE 2.—*Clinical Findings in Eight Children*

Data	Cases
Presenting complaint	
Large abdomen	6
Fatigue and exertional syncope	1*
"Pneumonia" with effusion	1*
Shortness of breath	5
Past history	
Lower respiratory infection	5
Pericardial effusion	1
Paracentesis	5
Etiology	
Tuberculosis suspected	2
Unknown	6
Physical findings	
Hepatomegaly	8
Ascites	6
Pleural effusion	3
Peripheral edema	2
Pulsation in veins of neck	3
Quiet heart (ticktock quality)	2

* Abdominal enlargement occurred subsequently.

duce a picture of progressive cardiac failure. failure.

Incidence.—The disease is rare in children. Rothstein [5,8] in 1934 reviewed the world literature and found 34 cases of both constrictive pericarditis and mediastinopericarditis that were treated surgically. Since then only scattered case reports have appeared together with larger surgical series concerning both adults and children.

Etiology.—White [7] has expressed the belief that virtually all instances of chronic constrictive pericarditis are the sequelae of previous tuberculous pericarditis which in most instances has gone unrecognized; the remaining cases follow either acute pericarditis of a pyogenic nature or conceivably

TABLE 3.—*Electrocardiographic, X-Ray and Laboratory Findings in Seven Children*

	Cases
QRS complexes of low amplitude	7
Inverted or diphasic T-waves	
Lead I	1
Lead II	6
Lead III	7
Auricular fibrillation	3
Venous pressure elevated (15.0 to 31.5 cm. of water)	5
Roentgen changes	
Calcification	3
Cardiac enlargement (slight)	3
Diminished pulsation (fluoroscopy)	2 (of 5)
Hepatic function	
Increased retention of sulfobromophthalein	6 (of 7)
Low serum proteins (<5 gm. per 100 cc.)	2 (of 7)
Albuminuria	
Transient	4
Persistent	2
Positive tuberculin reaction	1 (of 6)

traumatic hemopericardium. His experience has shown that rheumatic fever leaves pericardial adhesions but that these are neither massive nor constrictive. Two such cases were encountered in the records of the Mayo Clinic, one in a girl with rheumatic heart disease and the other in a boy with rheumatoid arthritis who developed pancarditis and died in cardiac failure. Neither displayed anatomic pericardial constriction and so both were excluded from this series.

TABLE 4.—*Results of Treatment in Eight Children*

	Cases
Surgical (pericardectomy)	7
Living and well (10 years, 9 years, and 16 months, respectively, after operation)	3
Died during or shortly after operation*	3
Died later (5 years)†	1
Nonsurgical	
Died 4 years after onset of symptoms‡	1

* Two patients, one operated on in 1942 and one in 1947, died in the operating room, apparently of cardiac arrest. One patient operated on in 1937 died 24 hours postoperatively.
† Patient operated on in 1937.
‡ Patient seen in 1931.

Pathologic Anatomy.—There occurs fibrous thickening of the epicardium, pericardium, or both, with or without adhesions and obliteration of the pericardial sac. The pericardium may be 1 to 5 mm. or more in thickness and fibrosis may vary in its distribution but generally involves the entire pericardium. Calcium, when present, may appear as granules or may be deposited in plaques or sheets. The myocardium may show inflammatory changes with scarring and atrophy.

Pathologic Physiology.—This may be summarized as inflow stasis and diminished cardiac output. The heart is unable to expand normally in diastole and may be unable to contract fully in systole. Either the right or the left chambers of the heart may be predominantly involved and there may be increased pressure in the larger peripheral veins, venae cavae, and right atrium. There may also be elevation of pressure in the pulmonary veins as reflected in the levels obtained by tracings of pulmonary-artery-wedge pressure during cardiac catheterization. Peripheral arterial systolic pressures have been reported to be low and

pulse pressures narrow, but in none of the cases in children described herein were there significant variations from normal values.

Symptoms.—These are much the same in children as in adults. White [7] has mentioned abdominal enlargement as the commonest presenting complaint. Edema, when present, is usually minimal and is far less striking than the abdominal findings. The patient may feel well or have no complaints beyond a feeling of fullness in the abdomen, with shortness of breath or dyspnea encountered less commonly. The experience in the present series of cases seems to corroborate these observations.

Signs.—The classic signs of chronic constrictive pericarditis are described as hepatomegaly and ascites, with or without peripheral edema, together with increased pulsation of the veins of the neck and quiet heart action. Beck [1] described the triad of chronic cardiac compression which bears his name, that is, ascites, high venous pressure, and quiet heart, the last-mentioned feature manifesting itself either by decreased precordial activity or diminished cardiac pulsation as evidenced fluoroscopically. Certainly the first two of his criteria were consistently demonstrated in the cases of the present series, but neither auscultatory nor fluoroscopic quiet heart has been found with equal frequency. Murmurs are characteristically absent.

The finding of calcification on roentgenographic examination is suggestive of constrictive pericarditis. Calcification is best demonstrated in the lateral and oblique views and may be evident only if the film is overexposed.[3] Calcification was seen in the minority of cases of the present series and this is consistent with the experience of others. Fluoroscopic examination is an important aid to diagnosis, but, as with calcification on roentgenograms, absence of evidence of calcification does not exclude its presence.

The electrocardiogram is probably the most valuable preliminary laboratory procedure available for study of this disease. The characteristic changes are QRS complexes of low amplitude in both the standard and unipolar precordial leads with low-amplitude, isoelectric, or inverted T-waves in all leads. The changes in the QRS complexes may be slight or marked and S-III often demonstrates the changes to the greatest extent. Auricular fibrillation occurs commonly.

Other laboratory procedures are mentioned for the sake of completeness. The excretion of sulfobromophthalein (Bromsulphalein) is often impaired, and transitory or persistent proteinuria is found. Both are common in right heart failure regardless of cause. Hypoproteinemia in children with this disease has been reported [3,6] and when present may be the result of impaired function of the liver coupled with loss of protein in the urine or in ascitic fluid.

Cardiac catheterization is a valuable procedure in study of the patient in whom constrictive pericarditis is strongly suspected but not conclusively demonstrated. White [7] has expressed the view that it offers a guide to surgical treatment when one side is found to be affected predominantly.

Treatment.—The treatment in virtually all cases is surgical. Subtotal pericardectomy and decortication of the heart offer the only hope for the progressively embarrassed heart and the failing patient. Response to operation may perhaps be influenced greatly by the condition of the myocardium at the time it is freed of its encasing pericardium. The secondary involvement of the liver is generally considered reversible even with passive congestion of long standing.

Summary and Conclusions

It appears that constrictive pericarditis as it was encountered in a series of eight children is not essentially different from the disease as it has been described in adults. The most frequently observed clinical features were abdominal fullness, due to hepatomegaly and ascites, and shortness of

breath. Peripheral edema and pleural effusion also occurred. Useful diagnostic procedures include electrocardiographic examination, measurement of venous pressure, and roentgenographic and fluoroscopic examinations. Cardiac catheterization is extremely valuable in confirming the diagnosis. Pericardectomy is the only effective treatment.

Mayo Clinic.

REFERENCES

1. Beck, C. S.: Two Cardiac Compression Triads, J. A. M. A., 104:714-716 (March 2) 1935.

2. Harrington, S. W.: Chronic Constrictive Pericarditis: Partial Pericardiectomy and Epicardiolysis in 24 Cases, Ann. Surg., 120:468-485 (Oct.) 1944.

3. Kuipers, F.: Chronic Constrictive Pericarditis Combined with Hypoproteinaemia, Arch. Dis. Childhood 30:285-290 (June) 1955.

4. Leaman, W. G., and Vastine, J. H., Jr.: Calcification of the Pericardium: Report of a Case in a Boy Aged 12, Am. J. Roentgenol. 43:35-41 (Jan.) 1940.

5. Rothstein, J. L.: Chronic Adhesive Pericarditis in Children and Its Surgical Treatment: Historical Aspect, Etiology, Pathology, Symptom Complex, Diagnostic Signs, Differential Diagnosis, Prognosis, Treatment, Arch. Pediat. 51:219-239 (April) 1934.

6. Stadler, H., and Stinger, D.: A Case of Pick's Syndrome as the Basis for a Study of Hypoproteinemia, J. Pediat. 18:84-94 (Jan.) 1941.

7. White, P. D.: Chronic Constrictive Pericarditis, Circulation, 4:288-294 (August) 1951.

8. Rothstein, J. L.: Chronic Adhesive Pericarditis in Children and Its Surgical Treatment: Report of Case of Pick's Disease in 12 Year Old Child: Abstracts from Literature of Cases Operated on, with Analysis of Results, Conclusions, Arch. Pediat. 51:288-309 (May) 1934.

Tuberculin Reactors Among Children in Highly Infected Chicago Areas

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Interest in tuberculosis in childhood, acquired during several years of observation of children in the Mantoux Clinic at Children's Memorial Hospital and the Pediatric Chest Clinic at Michael Reese Hospital led to a study of the incidence of tuberculin reactors among the clinic populations of these institutions. The pupils at one elementary school in close proximity to Michael Reese Hospital were also tested.

Organization of Study

A. Michael Reese Hospital.—The study ran over an 11-month period—June, 1952, to May, 1953. Selection of patients for testing was made at random in the General Pediatric Clinic, 15 to 20 children being tested at four clinic sessions weekly on Monday, Wednesday, Thursday, and Friday. Readings were made 96 hours later, except for the tests applied on Wednesday, which were read after 120 hours. The Vollmer patch test was used, with the patch applied to the intrascapular area to the left of the spine.

Parents were given typewritten instructions suggesting the following:

1. Keep patch dry.
2. Remove two days after being applied.
3. Return to clinic in four days.

Readings were made by one of two physicians and recorded as reactors and nonreactors on the basis of race and age.

All reactors were immediately given requisitions for chest x-rays. If the chest film revealed suspicious or definitely demonstrable pulmonary pathology, the patients were referred to the Pediatric Chest Clinic where they were closely observed and fluoroscoped at frequent intervals. A social worker made family follow-ups on these patients.

The reactors with negative chest x-rays were followed in the general pediatric clinic, x-rays of the chest being repeated at six-month intervals.

B. Children's Memorial Hospital.—The study ran over a four-month period—January through April, 1953.

All new patients admitted to the Baby Clinic and Medical Clinic were given Mantoux tests—one-tenth of a cubic centimeter of freshly prepared old tuberculin 1:1000 solution was used. Injections were made intradermally on the left forearm.

Tests were applied on the first three days of the week. Readings were made by one of two physicians 48 hours later. Tests were considered positive if there was an erythema and induration 5 mm. in diameter at the site of inoculation. All results were tabulated on the basis of race and age. All positive reactors were given requisitions for chest x-rays and referred to the Mantoux Clinic for follow-up.

C. Williams Elementary School.—Through the cooperation of the Board of Education, the Tuberculosis Institute of Chicago and Cook County, and the Chicago Health Department, the pupils of the Williams Elementary School were tuberculin tested. A letter was sent to the parents of each pupil requesting permission for their child to participate in the study. The returned letter bearing the parents' signatures was in the school 'nurse's possession before the child was tested.

The Vollmer patch test was applied in the same manner as described for the Michael

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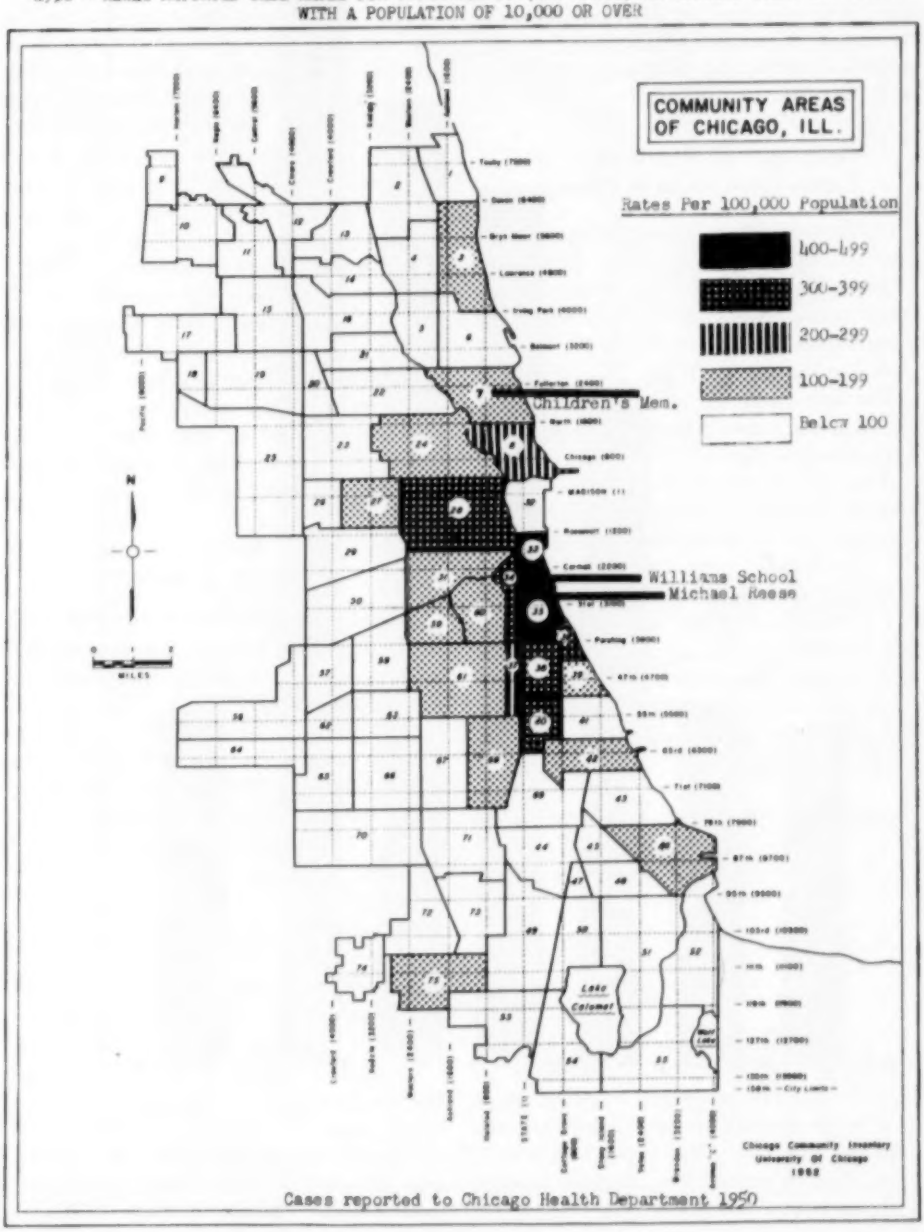
Reese Survey. Instructions were given to keep the patch dry. The patches were removed at school two days later. This was done in an effort to make a more accurate survey, for it was felt that in the clinic study an undeterminable number of patches may possibly have fallen off or been removed before the necessary 48 hours had elapsed. The tests were all read 96 hours after application.

1950 - NEWLY REPORTED CASE RATES FOR TUBERCULOSIS (ALL FORMS) IN CHICAGO COMMUNITY AREAS WITH A POPULATION OF 10,000 OR OVER



The Tuberculosis Institute of Chicago and Cook County supplied mimeographed forms to be returned to parents of nonreactors and another notification to parents of reactors suggesting available means of acquiring reliable follow-up study. The school nurse and personnel of the Municipal Tuberculosis Sanitarium Clinic played a very valuable part in the follow-up studies of these families.

Geographical Distribution of Tuberculosis Cases in Chicago

Observation of a map of Chicago divided into its 75 community areas reveals an unusually high tuberculosis case-rate incidence in the areas immediately surrounding these clinics and the elementary school included in the study (Map).

The case rates are calculated on a basis of new cases reported to the Chicago Health Department and on the 1950 Chicago census.

Area 35, in which Michael Reese Hospital is located, ranks second only to its neighbor, Area 33, in case rate incidence of tuberculosis per 100,000 population (areas of over 10,000 residents). Area 33 has an incidence of 459 new cases reported per 100,000 population, and Area 35 has 425. Michael Reese Hospital's Clinic population is drawn heavily also from other surrounding areas which rank high in case rate incidence, namely:

Area	Rank in Case Rate of Tuberculosis for Areas of Above 10,000 Population
35	3
38	4
40	6
34	7
37	8
60	11
31	12

The areas in the vicinity of Children's Memorial Hospital do not have quite as high a TBC rate incidence, however. Area 7, in which this institution is situated, ranks 16th and draws its clinic population heavily from Area 8, ranked 9th; Area 24, ranked 13th, and Area 3, ranked 14th (Graph 1).

Williams School is located in Area 34, which is listed seventh in case rate incidence of areas of over 10,000 population. A high percentage of the pupils reside in Area 35, which ranks second.

The population of 12 of the 16 highest ranking tuberculosis case-rate areas in the city contribute the greatest proportion of patients attending Michael Reese and Children's Memorial Hospital clinics. Forty-two and one-half per cent (42.5%) of new cases of tuberculosis reported to the Board of Health in 1950 came from these 12 areas which represented only 24% of the total Chicago population.

The results of this study are, therefore, not to be considered representative of the city as a whole, but it must be emphasized that they are, instead, a cross section of the communities most highly infected. The survey gives us a fair impression of the percentage of positive tuberculin reactors among children residing in highly infected Chicago community areas.

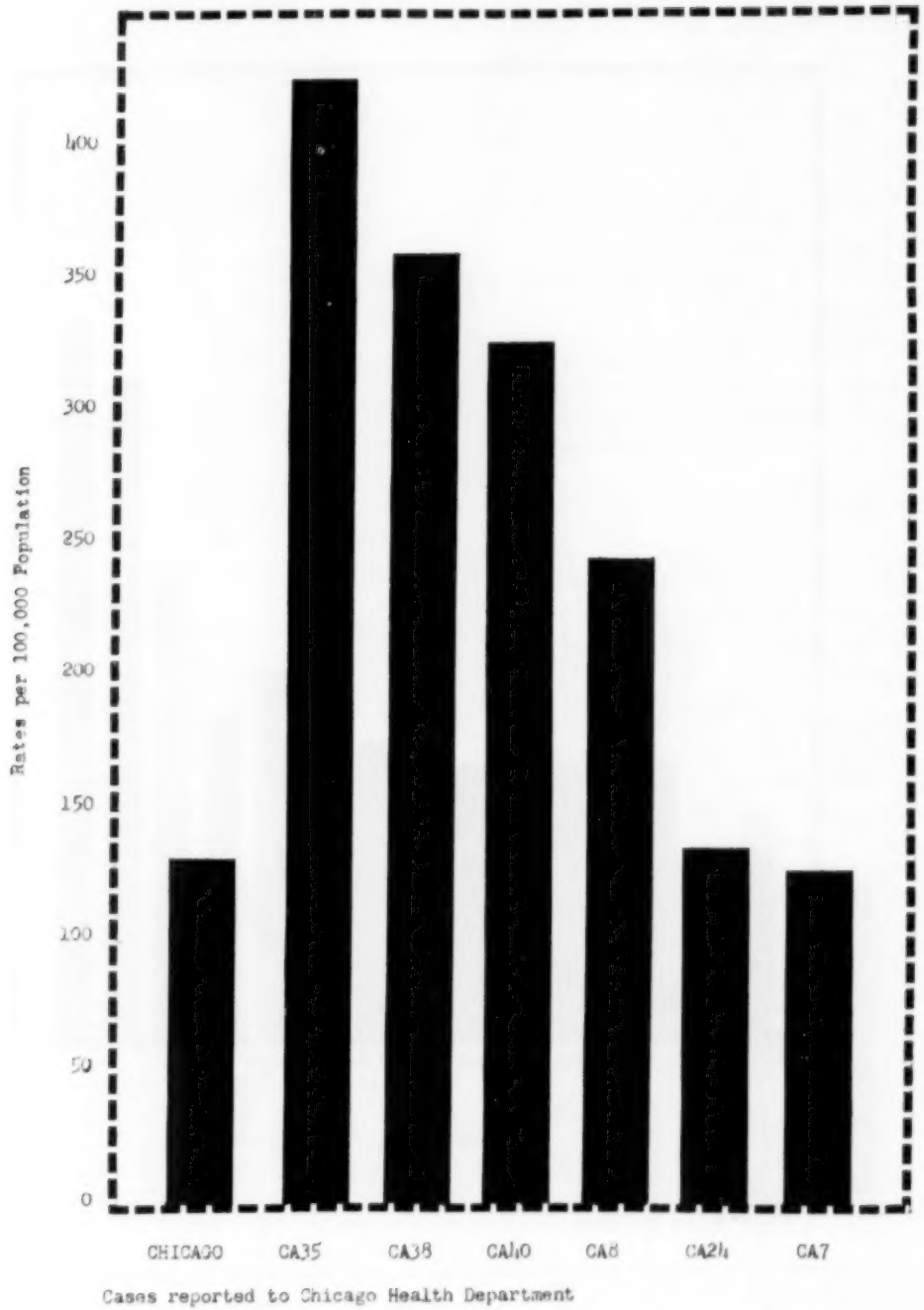
Results

A. Incidence of Reactors

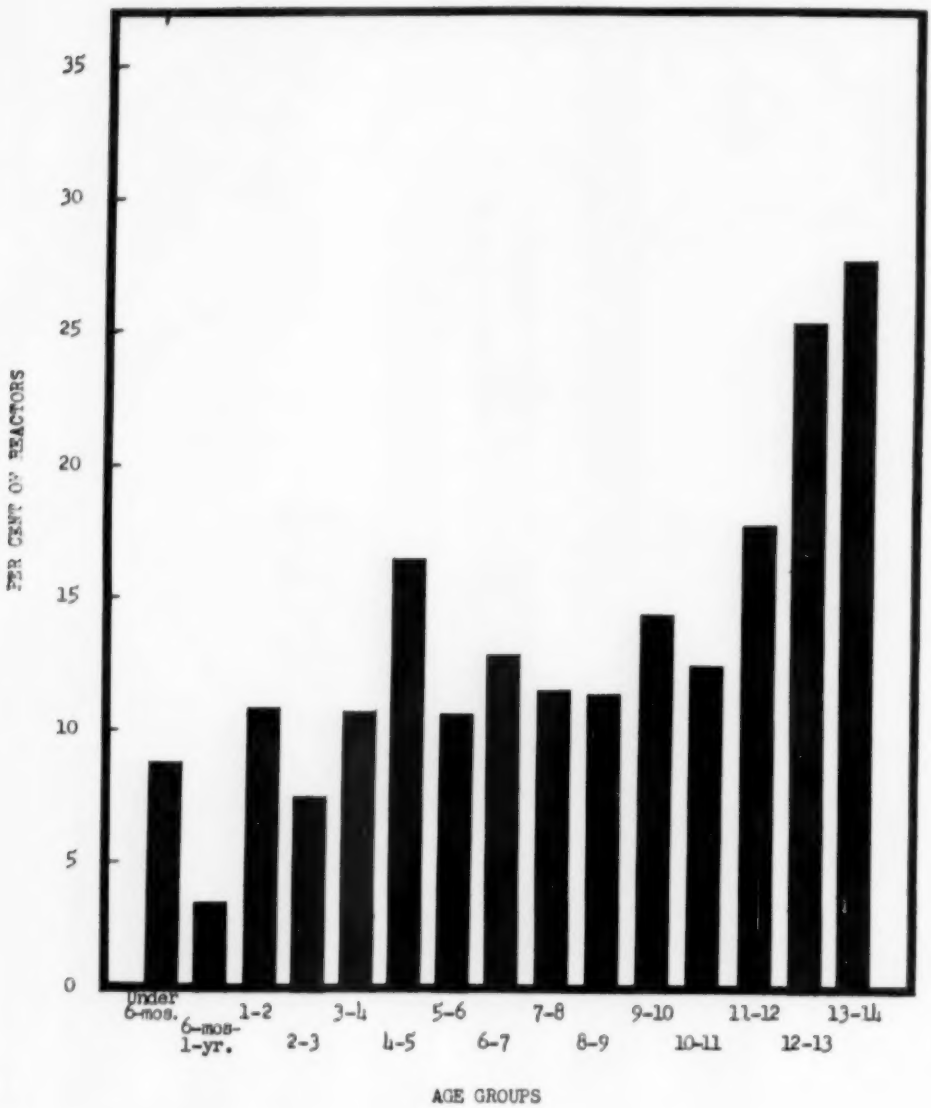
Group I.—Michael Reese Hospital Pediatric Clinic (Patch Test). There were 2057 children included in this survey; 32 of 360 white patients (8.8%) and 222 of the 1697 Negro patients (13.0%) were reactors. Negro children represented 82.5% and white children 17.5% of this study group. This total of 254 reactors among a group of 2057 tested represents a combined incidence of 12.3% reactors in the clinic population.

Age distribution is characterized by a gradual increase in incidence of reactors with increasing age, ranging from 3.4% at 6 months-1 year to 27.8% at 13-14 years (Table 1 and Graph 2).

Group II.—Children's Memorial Hospital Medical and Baby Clinic (Mantoux Test). There were 454 children included in this survey; 13 of 292 white patients (4.45%) and 19 of 162 Negro patients (11.7%) were reactors. Negro children represented



Graph 1.—The 1950 rates for newly reported cases of tuberculosis (all forms) in Chicago and six community areas in the city.



Graph 2.—Percentage of reactors among children patch tested at Michael Reese Hospital by age groups, June, 1952—May, 1953.

TABLE 1.—*Number of Children Patch Tested with Number and Per Cent of Reactors at Michael Reese Hospital by Age Groups, June, 1952-May, 1953*

Age Groups	Total Tested	Reactors	
		No.	Per Cent
Under 6 mo.	23	2	8.7
6 mo. to 1 yr.	148	5	3.4
1 to 2	212	23	10.8
2 to 3	229	17	7.4
3 to 4	196	21	10.7
4 to 5	189	31	16.4
5 to 6	214	23	10.7
6 to 7	155	20	12.9
7 to 8	123	14	11.4
8 to 9	122	14	11.5
9 to 10	105	15	14.3
10 to 11	105	13	12.4
11 to 12	73	13	17.8
12 to 13	91	23	25.3
13 to 14	72	20	27.8
Total	2057	254	12.3

82.5% Negro children.
17.5% white children.

only 36% and white children 64% of this study group. This total of 32 reactors among 454 youngsters tested represents a combined incidence of 7.0% reactors in the clinic population.

Age distribution is characterized also by a gradual increase in incidence of reactors in direct proportion to increasing age, ranging from 2.6% at 1-2 years to 14.3% at 11-12 years (Table 2 and Graph 3).

Group III.—Williams Elementary School. The school survey offered some advantages over the clinic groups in control of statistics, for here was a so-called "captive" group where we had an opportunity to apply, remove, and read the results of the patch tests without necessitating an additional return visit to the clinic. The patches were applied on May 25, 1953, an unusually warm spring day with a high temperature reading of 88F. Low for the day was 63F.

There were 799 pupils included in this study between the ages of 5 and 15 years; all were Negroes. Seven hundred ninety-nine patch tests were applied, and it was discovered 48 hours later, at the time planned for removal, that 162 of the children were patchless. These tapes had either fallen off as result of activity and/or perspiration, or had been removed prematurely. This represented a loss of 20% of the original group.

Six hundred thirty-seven patches were removed, and of this group 75 (11.8%) pupils reacted to tuberculin. Forty-six of the six hundred thirty-seven children were absent on the day of reading and were checked and reported by the school nurse subsequently. Five of these absentees were reactors. This small group was reported as a unit without age breakdown.

The percentage of reactors based on age distribution ranged from 5.6% in the kindergarten class to 20.8% in the upper grades (Table 3 and Graph 4).

The 75 reactors are being x-rayed periodically and followed closely by either their private physician or the Municipal Tuberculosis Sanitarium Clinic.

B. Incidence of Demonstrable Primary Tuberculosis

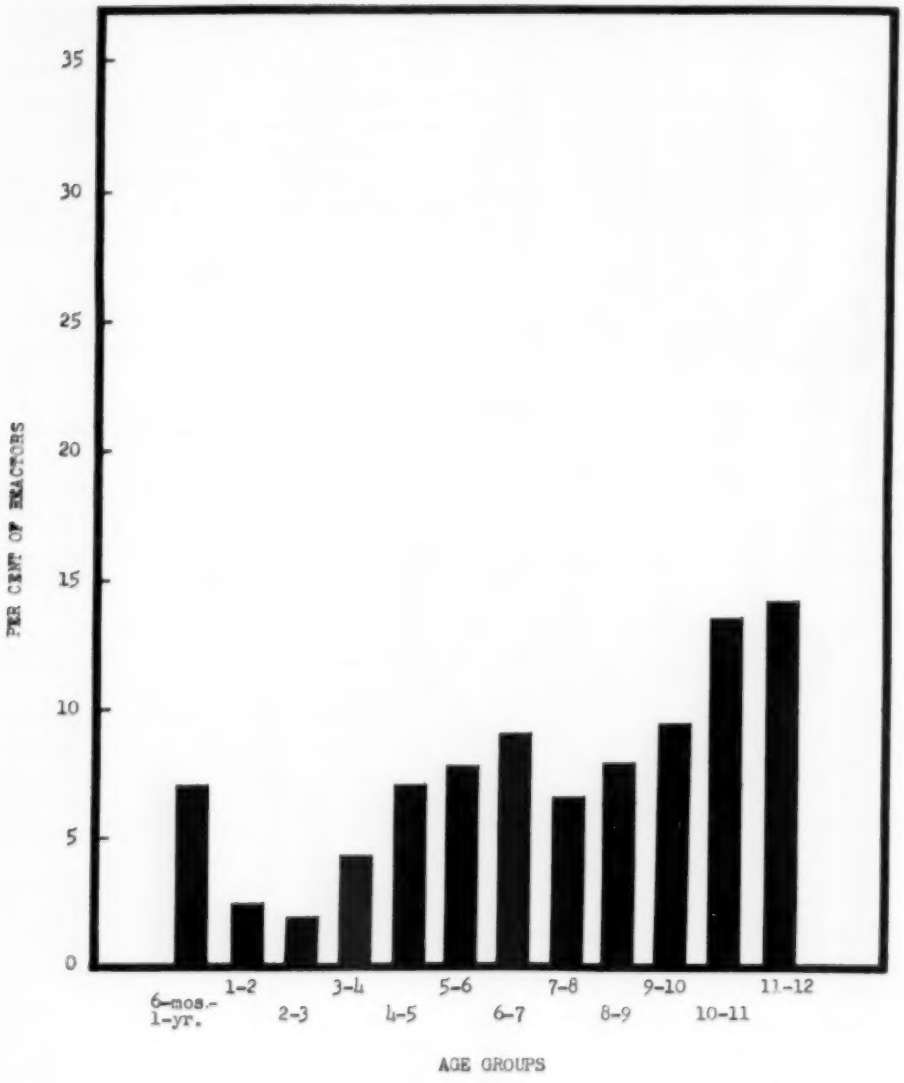
Group I.—Michael Reese Hospital. Ten of thirty-two white reactors (31.2%) had demonstrable primary tuberculous lesions. Only one of this number was considered to have active acute inflammatory lesions in the lung and tracheobronchial lymph nodes. The other nine had calcified parenchymal and lymph-node lesions.

Fifty-seven of two hundred twenty-two Negro reactors (25.6%) had demonstrable primary tuberculosis. Fourteen of this number were considered to have active acute inflammatory lesions in the lungs and

TABLE 2.—*Number of Children Mantoux Tested with Number and Per Cent of Reactors at Children's Memorial Hospital by Age Groups, January, 1953-May 1953*

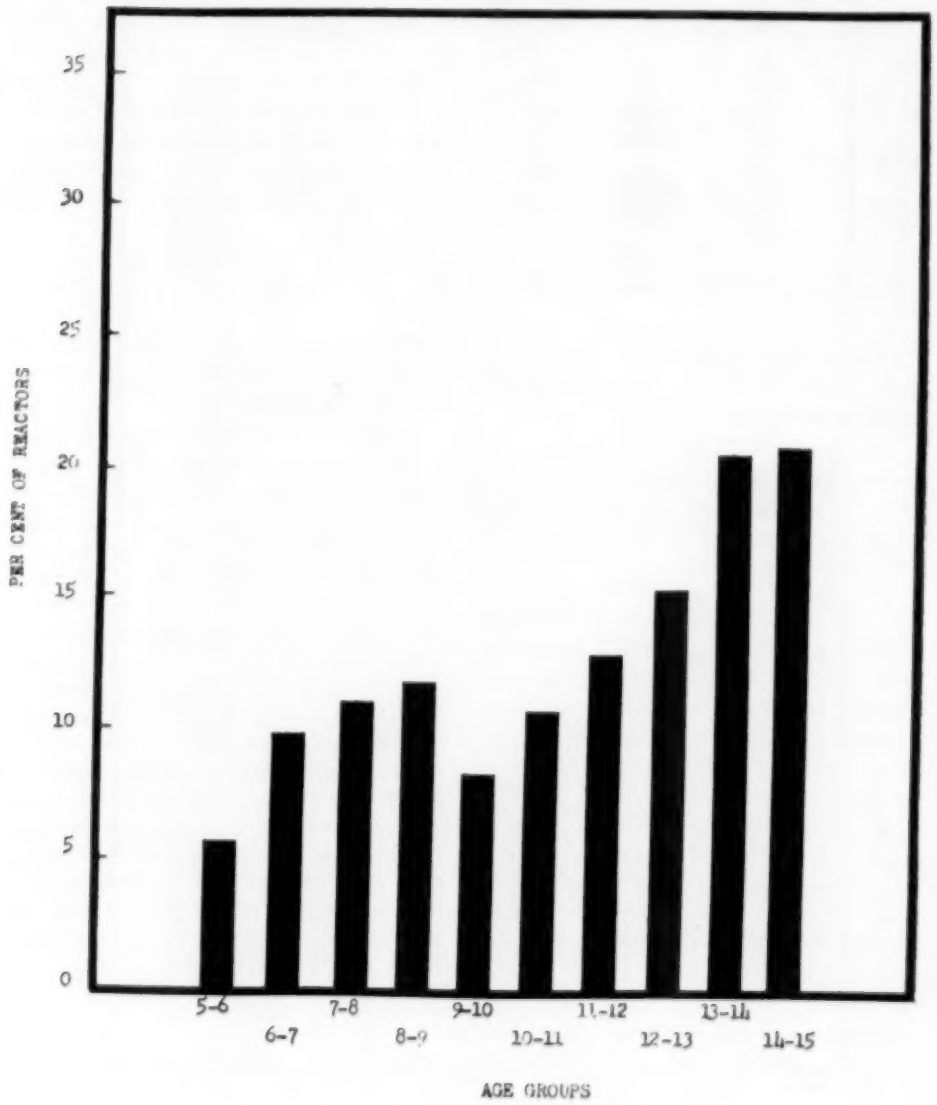
Age Groups	Total Tested	Reactors	
		No.	Per Cent
Under 6 mo.	6	1	16.7
6 mo. to 1 yr.	28	2	7.1
1 to 2	38	1	2.6
2 to 3	51	1	2.0
3 to 4	45	2	4.4
4 to 5	56	4	7.1
5 to 6	63	5	7.9
6 to 7	33	3	9.1
7 to 8	45	3	6.7
8 to 9	25	2	8.0
9 to 10	21	2	9.5
10 to 11	22	3	13.6
11 to 12	21	3	14.3
Total	454	32	7.0

O.T. 1:1000.
36% Negro children.
64% white children.



1. Old Tuberculin, 1:1000.

Graph 3.—Percentage of reactors among children Mantoux tested[1] at Children's Memorial Hospital by age groups, January, 1953—May, 1953.



100% Negro

Graph 4.—Percentage of reactors among children patch tested at Williams School by age groups, May 25, 1953.

TABLE 3.—*Number of Children Patch Tested with Number and Per Cent of Reactors at Williams School by Age Groups, May 25, 1953*

Age Groups	Total Tested	Reactors	
		No.	Per Cent
5 to 6 years	54	3	5.6
6 to 7	72	7	9.7
7 to 8	73	8	11.0
8 to 9	77	9	11.7
9 to 10	73	6	8.2
10 to 11	75	8	10.7
11 to 12	47	6	12.8
12 to 13	33	5	15.2
13 to 14	39	8	20.5
14 to 15	48	10	20.8
Total	591	70	11.8
Absentees*	46	5	
Total	637	75	11.8

100% Negro.
* 46 absentees reported as a single group (not broken down on basis of age).

tracheobronchial lymph nodes. Forty-three had calcified or caseous parenchymal and lymph-node lesions.

The total of 67 demonstrable primary lesions among 254 reactors in the Michael Reese group represents a percentage of 26.4 of the reactors, and 3.2% of the total group tested (Table 4).

Ninety-three per cent (93%) of the lesions in these children were of the intrathoracic variety. Phlyctenular conjunctivitis and cervical adenitis made up the 7% extrathoracic lesions.

Adult contacts were discovered or known in 38 (56%) of the 67 patients with demonstrable primary tuberculosis.

Group II.—Children's Memorial Hospital. Three of thirteen white reactors (23.1%) had demonstrable primary tuberculous lesions. Each of these had calcified parenchymal and lymph-node involvement.

Six of nineteen Negro reactors (31.5%) had demonstrable primary tuberculosis. One infant in this group had active acute inflammatory lesions in lungs and tracheobronchial lymph nodes. The remaining five had calcified or caseous parenchymal and lymph-node lesions.

The total of nine demonstrable primary lesions among 32 reactors in the Children's Memorial group represents a percentage of 28.1 of the reactors and 1.9% of the total group tested.

Eighty-nine per cent of the lesions in these children were of the intrathoracic variety.

Adult contacts were discovered or known in (44%) of the patients with demonstrable primary tuberculosis.

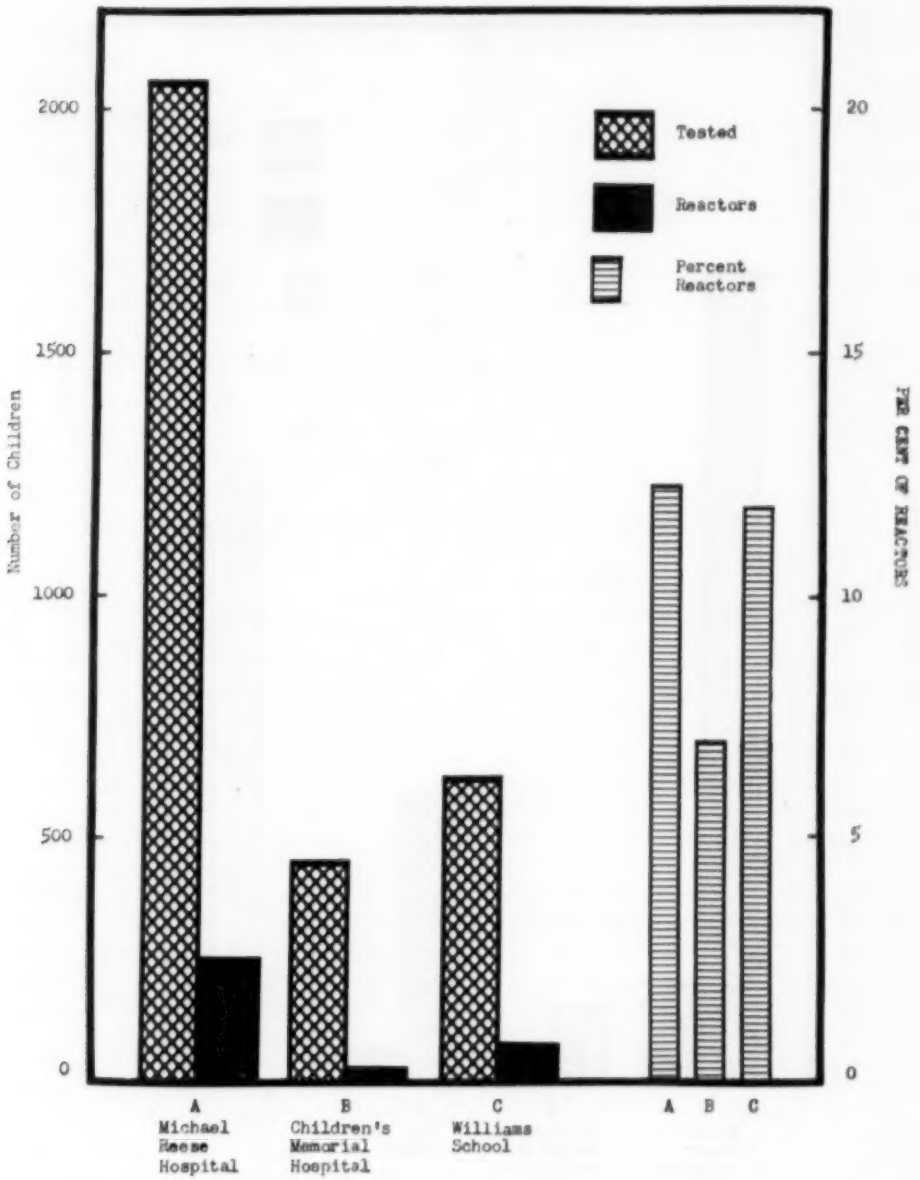
Group III.—Williams Elementary School. Through the perseverance of the school nurse all 75 reactors had chest x-rays made at the Municipal Tuberculosis Sanitarium Clinic of Mercy Hospital. Two cases of active pulmonary tuberculosis were discovered. These active cases were not known to any physician or clinic before the school patch testing was done. They were excluded from school by the Chicago Department of Health. One was hospitalized at the Municipal Tuberculosis Sanitarium, and the other was put at bed rest at home and given intermittent streptomycin and chemotherapy. No contact was found in the first case. However, in the second case a maternal aunt was found to have an active reinfection pulmonary tuberculosis and was subsequently hospitalized at the Municipal

TABLE 4.—*Number and Percentage of Demonstrable Primary Tuberculosis Among Tuberculin Reactors*

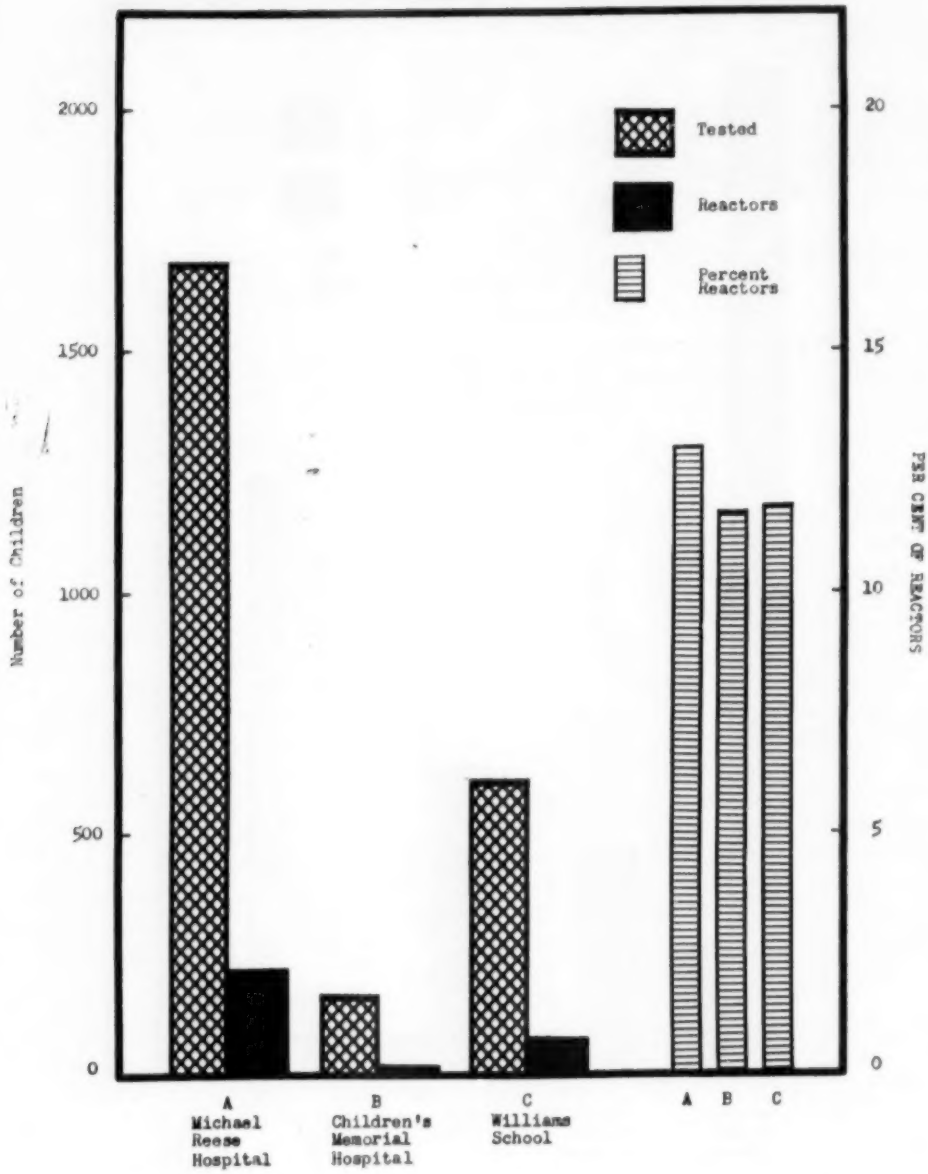
Survey Group	Total			White			Negro		
	Number Reactors	Demonstrable Primary TB		Number Reactors	Demonstrable Primary TB		Number Reactors	Demonstrable Primary TB	
		Number	Per Cent		Number	Per Cent		Number	Per Cent
Michael Reese Hospital	254	67	26.4	32	10	31.2	222	57	25.6
Children's Memorial Hospital	32	9	28.1	13	3	23.1	19	6	31.6
Total	286	76	26.6	45	13	28.9	241	63	26.1

The 67 children with demonstrable primary tuberculosis represent 3.2% of the total Michael Reese group tested.

The nine children with demonstrable primary tuberculosis represent 1.9% of the total Children's Memorial group tested.



Graph 5.—Number of children tested with number and percentage of reactors in three survey groups.



Graph 6.—Number of Negro children tested with number and percentage of reactors in three survey groups.

TABLE 5.—*Number of Children Tested and Percentage of Reactors in Three Survey Groups by Race*

Survey Group	All Races			White			Negro		
	Number Tested	Number Reactors	Per Cent Reactors	Number Tested	Number Reactors	Per Cent Reactors	Number Tested	Number Reactors	Per Cent Reactors
Michael Reese Hospital (Patch)	2057	254	12.3	360	32	8.8	1697	222	13.0
Children's Memorial Hospital (Mantoux)	454	32	7.0	292	13	4.5	162	19	11.7
Williams School (Patch)	637	75	11.8	....	....	....	637	75	11.8
Total (Patch-Mantoux)	3148	361	11.5	652	45	6.9	2496	316	12.6

Tuberculosis Sanitarium. This child's five siblings were also found to be reactors.

Summary of the Three Groups Tested

At Michael Reese Hospital the occurrence of reactors among the population of the General Pediatric Clinic was 12.3%. The Children's Memorial Hospital reactors represented 7.0% of the total group tested. At Williams School the incidence of reactors was 11.8% (Graph 5).

It is interesting to note that if these figures are broken down on the basis of race, the incidence of reactors among Negro children in each group is almost identical, i. e., Group I, 13%; Group II, 11.7%, and Group III, 11.8% (Graph 6).

The difference, however, in the occurrence of reactors among the white children is quite striking, 8.8% in Group I and only 4.5% in Group II, and accounts for the low total of 7.0% reactors at Children's Memorial Hospital. This, I believe, can partly be explained by the fact that a considerable number of the white children tested at Michael Reese Hospital were foreign born and had dwelled in displaced-person camps in Europe during their early years, immediately after World War II. The great majority of children with this background who were tuberculin tested in this country and elsewhere have proved to be positive reactors.[20] Even though the number of cases of demonstrable primary tuberculosis in this clinic material is small, the higher incidence of visible pulmonary lesions among the white children in the Michael Reese group may also be explained on the same basis.

Another condition influencing the low total of 7% reactors at Children's Memorial is the much lower proportion of nonwhite patients involved in the survey. Here the socioeconomic factor is very significant.

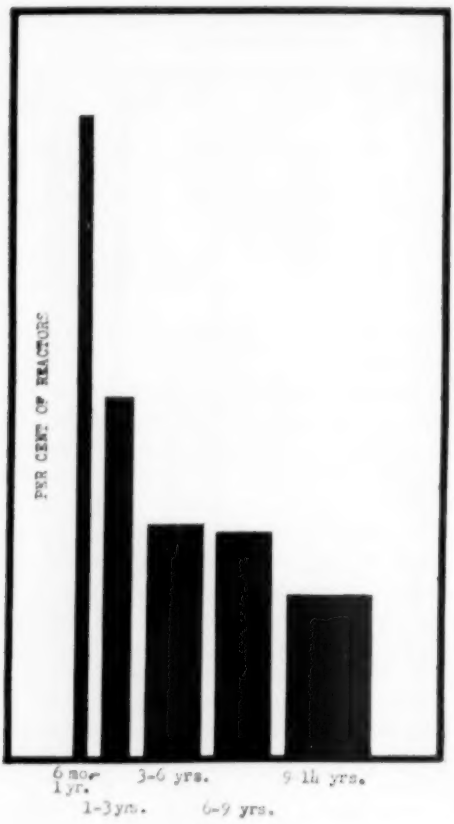
A summary of tuberculin reactors on the basis of race, tested by both methods, reveals the incidence of white reactors in the two clinic units to be 6.9% and the nonwhites in the three surveys to be 12.6%. This supports the generally accepted contention that primary tuberculosis is twice as common among nonwhites in urban communities as it is among the white population (Table 5).

The incidence of demonstrable primary tuberculosis among positive reactors in the two clinics was 26%. This figure compares closely with other reports in the literature.[14,23] When these statistics are broken down according to age, it is noted that the highest percentage of demonstrable primary tuberculosis is found among the youngest

TABLE 6.—*Percentage of Demonstrable Primary Tuberculous Lesions Among Positive Reactors at Children's Memorial and Michael Reese Hospitals by Age Groups*

Age Group	Reactors	Demonstrable Primary Lesions	
		Number	Per Cent
6 mo.-1 yr.	7	5	71
1-3 yr.	42	17	40
3-6 yr.	86	23	26
6-9 yr.	56	14	25
9-14 yr.	92	17	18
Total	283*	76	26

* Three reactors under 6 months not included.



Graph 7.—Percentage of demonstrable primary tuberculous lesions among positive reactors at Children's Memorial and Michael Reese hospitals by age groups.

group of reactors, and this incidence varies inversely with increasing age. The infant's low resistance to tuberculosis is well known.

Lincoln[20] reported the occurrence of demonstrable primary tuberculosis in 80% of the infant reactors in her chest clinic. In this study 71% of the infants (6 months-1 year) who reacted to tuberculin showed a demonstrable primary lesion (Table 6 and Graph 7).

Comments

The methods of tuberculin testing selected for use in the clinics were routine procedures at these institutions. The Vollmer patch test was chosen for the public school survey because of its simplicity and the probability of acquiring a greater number of permits from parents if the intradermal injection was avoided.

Many articles referring to the correlation of accuracy in comparative studies on the Vollmer patch and Mantoux tests appear in the literature. The great majority support the reliability of the patch test in any large-scale tuberculin testing program.[3-12] The per cent of agreement between the two methods varies from 92 to 99 in these studies.

It is important to recognize that in a specific case where a child is suspected of having tuberculosis, the preferred diagnostic tuberculin test should be intradermal.

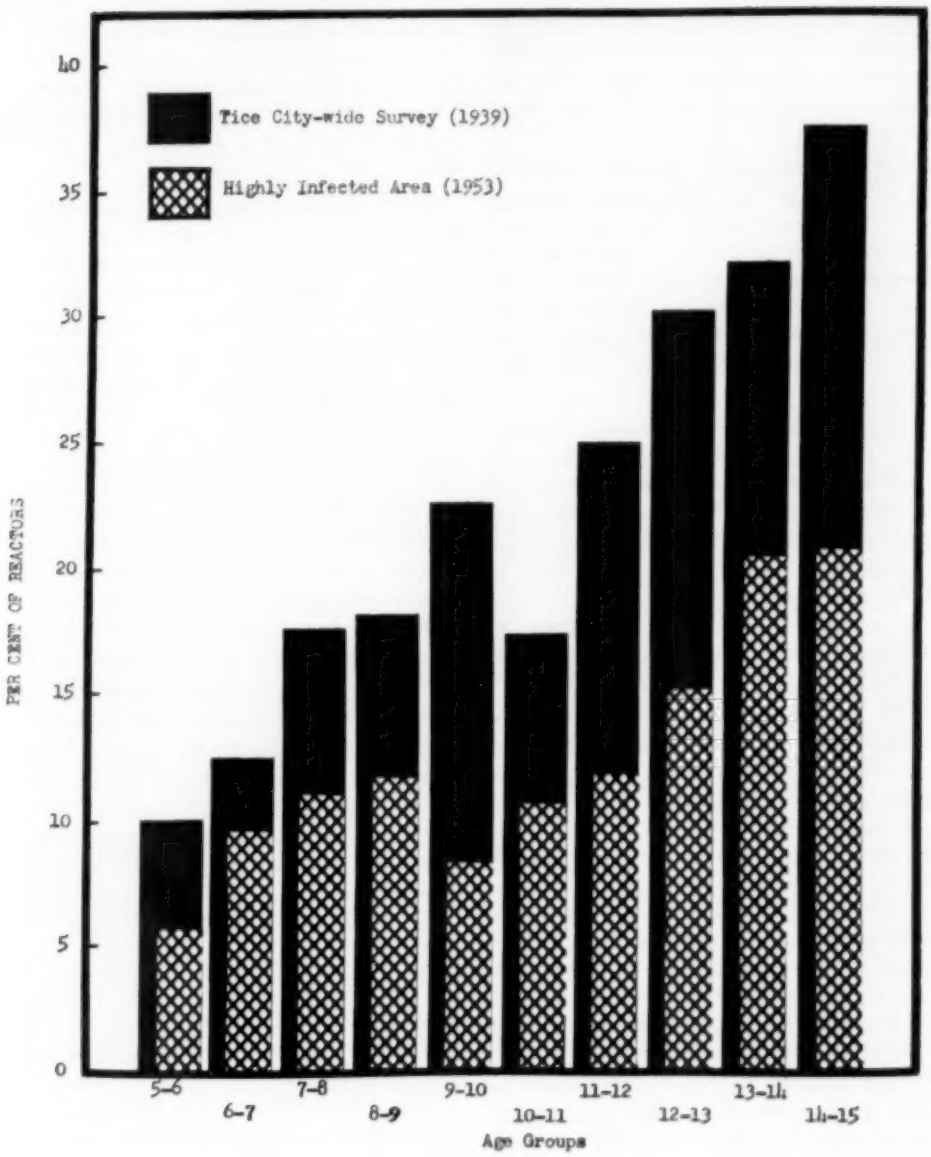
The patch and Mantoux tests compared favorably in closely similar groups in this survey. Among the Negro children tested, 12.2% reacted positively to the patch test and 11.7% gave positive reactions to the Mantoux, a correlation of 96%.

For the sake of accuracy in using the patch test and judging from our experience, it seems imperative that the tapes be removed by the examiner 48 hours after application.

There is a scarcity of reports on occurrence of tuberculin reactors among pediatric clinic populations; the great majority of published material considering this age group throughout the United States has come from studies made in the elementary schools. For information regarding the in-

TABLE 7.—*Comparison of Tuberculin Reactors Among Negro Children in a Chicago City-Wide Survey (1939) with Those in Highly Infected Chicago Community Areas (1953)*

Age Groups	Per Cent of Reactors	
	Tice Survey 1939	Williams School 1953
5-6	10.0	5.6
6-7	12.4	9.7
7-8	17.6	11.0
8-9	18.2	11.7
9-10	22.8	8.2
10-11	17.2	10.7
11-12	25.0	12.8
12-13	30.3	15.2
13-14	32.2	20.5
14-15	37.5	20.8



*Tice - American Review of Tuberculosis 43:96, 1941

Graph 8.—Comparison of tuberculin reactors among Negro children in a Chicago city-wide survey (1939)* with those in highly infected Chicago community area (1953).

fants and preschool children we must rely on the family physician, pediatrician, and on clinic testing. For school-age children, testing within the schools has definite advantages, for we are dealing with a so-called "captive group" and thus eliminate the uncertainty of return visits to private physicians or clinics.

Further emphasis on repeated testing of all children, particularly negative reactors, at frequent intervals so that one is in a position to recognize recent converters has been advocated by several leaders in the field of tuberculosis, for specific chemotherapy is now advised by some as the treatment of choice of the recent converter.[16,17]

Nelson states that the incidence of positive reactors at all ages has decreased markedly within recent years. In contrast to rates of 80% to 90% among adolescents and young adults in surveys of urban population 15 to 20 years ago, rates at these ages now are mainly in the 5% to 20% range. Rates of reactors among infants and children have decreased proportionately.[18]

In support of this impression it is enlightening to compare the occurrence of reactors in Tice's city-wide survey of Chicago school children made in 1939[14] with the incidence of reactors at Williams Elementary School, representing a highly infected Chicago area in 1953. The present survey was confined entirely to areas of high mortality and gives an unduly high reaction rate and yet, by comparison with the study made 14 years before, indicates a very significant reduction in incidence of reactors (Table 7 and Graph 8).

Considerable progress has been made by the Chicago tuberculosis control program in diminishing the prevalence of active reinfection tuberculosis in the environment of the city's infants and school children; however, there is still much to be desired. No city-wide tuberculin testing survey of our school children has been made since 1939. Studies of the rate of reactors in suburban schools have been made annually by the Tuberculosis Institute of Chicago and Cook County under the supervision of Dr. Julius Novak. His 1953 statistics revealed 3%-5% reactors among elementary pupils[23] and in Petter, Lake County, Ill., 7% reactors. There is, at this time, every indication for and great need of a repetition of Tice's work in the city schools.

Smith suggests as one of the criterion for determining control of tuberculosis in a given area a 5% or less incidence of positive tuberculin reactors in the school population.[22] Considering this goal, it is apparent from Novak's statistics that our suburban areas approach having tuberculosis under control. I should judge from available evidence that the city-wide picture in Chicago proper would closely approximate the control requisite of 5% reactors among the elementary-school population. However, it is very apparent that much tuberculosis control work, including conscientious case finding activity, must be concentrated in the highly infected areas before they too can be considered within controlled levels. Only after tuberculosis is under control can we begin to make plans for its eradication.

Levine, in discussing the question, "Can tuberculosis be eradicated in school children?," suggests that such can only occur when we have eradicated the disease in our communities by the elimination of infection. There is only one certain immunity to tuberculosis—the absence of tubercle bacilli.[19]

Every case-finding method must be utilized to accomplish this end. Myers emphasizes that no community can afford to maintain an old-fashioned tuberculosis control program which neglects the children. It is giving careful attention to tuberculosis among children which modernizes any true tuberculosis control program.[15] The tuberculin test is our most effective and valuable weapon in any such undertaking and with the declining incidence of positive reactors, tuberculin testing at all age levels is ever gaining in importance.

Summary

Incidence of reactors: Michael Reese Hospital, 12.3%; Children's Memorial Hospital, 7.0%; Williams School, 11.8%. These represent the incidence of reactors in essentially the most highly infected Chicago community areas.

Patch test and Mantoux compared favorably in closely similar groups (Negroes in both groups showed an incidence of reactors of 12.2% and 11.7%, respectively).

Negro reactors, all groups, 12.7%; white reactors, Children's Memorial and Michael Reese hospitals, 6.9%.

Incidence of reactors increased in direct proportion to the age of youngsters in each group studied.

Demonstrable primary tuberculosis was detected in 26.6% of reactors.

Pulmonary lesions represented 93% of the total demonstrable tuberculous lesions in the clinic groups.

Two unknown cases of active primary tuberculosis were discovered in the school study.

In using the patch test in a tuberculosis survey, it is imperative, for the sake of accuracy, that the patches be removed by the examiner in all cases.

During the past 15 years there apparently has been a gradual decrease in the amount of active tuberculosis in the environment of Chicago's infant, preschool and elementary-school child. However, there is still great need for considerable improvement.

Wider use of tuberculin testing programs at all age levels is the best method known at the present time to hasten the eradication of tuberculosis.

Drs. Lawrence Breslow and Sidney Mannell cooperated in this study. Technical assistance was accorded by the Tuberculosis Institute of Chicago and Cook County.

REFERENCES

1. Martin, D. W., and Arena, J. M.: Relationship of Race to the Incidence of Diphtheria and to Schick, Tuberculin, and Wasserman Tests in Hospitalized Children, J. Pediat. 32:530, 1948.

2. Myers, J. A.: Tuberculosis Among Children and Adults, Ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1951, p. 148.

3. Hughes, J. G.: The Vollmer Tuberculin Patch Test: Evaluation of Its Relative Sensitivity, J. Pediat. 16:171, 1940.

4. Pearse, A. J.; Fried, R. I., and Glover, V. A.: The Tuberculin Patch Test and Mantoux Intradermal Test: A Comparative Study in 700 School Children, J. A. M. A. 114:227, 1940.

5. Craig, J. D., and Scheuer, L. A.: The Vollmer Patch Test as a Routine Procedure, Arch. Pediat. 57:177, 1940.

6. Goldstein, H.: Comparative Study and Significance of the Tuberculin Patch and Mantoux Test in Children, J. Pediat. 27:245, 1945.

7. Vollmer, H., and Goldberger, E. W.: New Tuberculin Patch Test, Am. J. Dis. Child. 54:1019, 1937.

8. Vollmer, H.: Value of Tuberculin Patch Test in Case Finding, J. Pediat. 16:627, 1940.

9. Dormer, B. A.; Friedlander, J.; Wiles, F. J., and Schaffer, R.: Tuberculin Patch Test: A Comparison with Mantoux Intracutaneous Tests, Am. Rev. Tuberc. 48:324, 1943.

10. Crimm, P. D.; Cookson, H. N., and Broadbent, M.: Patch and PPD Tests and X-Ray Correlation, Am. Rev. Tuberc. 43:799, 1941.

11. Fineman, A. H., and Blair, G.: Evaluation of Tuberculin Patch Test, Am. J. Dis. Child. 60: 631, 1940.

12. Neiman, I. S.; Rosenthal, S. R., and Motel, W. G.: Tuberculin Patch Test (Vollmer) on BCG Vaccinated and Control Children, J. Pediat. 19:540, 1941.

13. Nelson, W. E.: in Brenneman's Practice of Pediatrics, Vol. 2, edited by Irvine McQuarrie, Hagerstown, Md., W. F. Prior Company, Inc., 1948, chap. 28, p. 14.

14. Tice, F.: Tuberculin Testing in Chicago Schools, Am. Rev. Tuberc. 43:96, 1941.

15. Myers, J. A.: Tuberculosis Among Children and Adults, Ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1951, p. 318.

16. Waring, J. J.: Present Day Treatment of Pulmonary Tuberculosis, Chicago M. Soc. Bull. 55:318, 1952.

17. Lichtenstein, M. R.: Symposium on Primary Tuberculosis in Children: Criteria for Sanatorium Admission for Children with Tuberculosis, Proc. Inst. Med. Chicago 19:145, 1952.

18. Myers, J. A.: Tuberculosis Among Children and Adults, Ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1951, p. 503.

19. Levine, E. R.: Can Tuberculosis Be Eradicated in School Children?, J. School Health 21:37, 1951.

20. Lincoln, E. M.: Symposium on Tuberculosis: Course and Prognosis of Tuberculosis in Children, Am. J. Med. 9:623, 1950.

21. Van Leent, J. P., and Hopkins, P. F.: Report of a Mantoux Survey of "Displaced Persons" Migrant Children, M. J. Australia 1:673, 1951.

22. Smith, D. T.: The Elimination of Tuberculosis from the Midwestern States in the Next 50 Years, Dis. Chest 26:615, 1954.

23. Report on Tuberculin Testing of Suburban School Population (1953), Tuberculosis Institute of Chicago and Cook County, Nov. 4, 1954.

24. Sweeny, cited by Myers.

Abstracts from Current Literature

Acta pædiatrica, Stockholm

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Renal Thrombosis in the Newborn: Report of a "Primary" Case Successfully Treated by Surgery. E. Tveteras and P. Rudstrom.—p. 545.

The Nature of Crystalline Material in Tissues of Lignac-Fanconi's Disease. H. S. Baar and Stella Baar—p. 551.

Albright's Syndrome: A Brief Survey and Report of a Case in a Seven-Year-Old Girl. Ulla Arlien-Soborg and Torben Iversen.—p. 558.

Cat as Possible Source of Infection in a Case of Congenital Toxoplasmosis. P. H. F. Borgen, S. Erichsen, and B. Standal.—p. 569.

Morphology of the Pancreas and Glucose Tolerance in Biliary Fistula, in Common Bile Duct Obstruction and After Ligation of Pancreatic Duct. Yngve Larsson.—p. 577.

The Histopathologic Changes in the Myenteric Plexus of the Pylorus in the Hypertrophic Pyloric Stenosis of Infants (Pylorospasm). Hilma Alarotu.—p. 579.

Proceedings of Pediatric Societies:

Pediatric Society of the South of Sweden.—p. 582.

Section of Pediatrics and School Hygiene of the Swedish Medical Society.—p. 583.

Tetracycline Treatment of Whooping-Cough.—The literature concerning the use of antibiotics in pertussis is reviewed including the favorable results from the use of tetracycline published by Wood, Dowling, and others. The present study reports results of treatment of 54 cases of pertussis controlled by a series of 42 cases given a placebo, cases being assigned alternately to either treatment or control groups irrespective of sex, age, and stage of illness.

The dosage was 30 mg/kg. body weight daily, divided into four doses and continued for seven days. The effect of treatment was assessed by carefully recorded number of paroxysms and "whoops." Cases were divided into two groups: Group I, in which symptoms had been present for two weeks prior to admission, and Group II, in which symptoms had been present more than two weeks. The results obtained indicated that in neither group was there any demonstrable effect of tetracycline therapy and the rate of complications was the same in both the treated and control series. There were few untoward effects, although transient diarrhea occurred in 14%.

American Heart Journal, St. Louis

52, No. 3 (Sept.) 1956

* The Genesis of the "Presystolic" Murmur in Mitral Stenosis. Henry T. Nichols, William Likoff, Harry Goldberg, and Morton Fuchs.—p. 379.

Coarctation of the Pulmonary Artery. John E. Coles, and Weldon J. Walker.—p. 469.

52, No. 4 (Oct.) 1956

The Importance of Positive T Waves in the Right Precordial Electrocardiogram During the First Year of Life. Robert F. Ziegler.—p. 535.

Electrocardiographic and Hemodynamic Correlation in Atrial Septal Defect. Weldon J. Walker, Thomas W. Mattingly, Byron E. Pollack, David B. Carmichael, Thomas W. Inmon, and Ralph H. Forrester.—p. 547.

* Observation on the Direct Effect of Digoxin on Renal Excretion of Sodium and Water. Albert L. Hyman, William E. Jaques, and Edward S. Hyman.—p. 592.

The Genesis of the "Presystolic" Murmur in Mitral Stenosis.—The classic view is that the "presystolic" murmur of mitral stenosis results from the flow of blood across a stenotic mitral valve orifice during the latter part of atrial contraction. The authors present evidence for a different genesis of this murmur.

In their observations during intracardiac surgery they noted that the "presystolic" murmur was present in those patients in whom the commissures of the mitral valve were, in part, fused, while the central portion of each leaflet was free to bulge either into the ventricular chamber in diastole or into the atrial chamber in systole. If both the leaflets on the mitral valve, as well as the commissures, were fixed and inflexible, a mid-diasotlic murmur rather than a "presystolic" murmur was present.

In those patients with a "presystolic" murmur in whom the central portion of the leaflets of the mitral valve was free to move, it was possible to feel strong vibrations particularly over the septal leaflet when this leaflet bulged into the atrium in the early part of isometric ventricular contraction. Gentle finger pressure over the leaflet caused the "presystolic" murmur to disappear. The sharp first heart sound associated with the "presystolic" murmur occurred just at the instant that the intra-atrial displacement of the valve leaflet was abruptly concluded. Having defined the genesis of the mitral "presystolic" murmur, their observations further indicated that this murmur actually originated early in mechanical systole rather than in diastole. The disappearance of the "presystolic" murmur with the onset of atrial fibrillation is attributed to an associated reduced intraventricular displacement of the central portion of the leaflet during diastole resulting from the weak atrial contractions. The force necessary to produce intra-atrial displacement of the leaflets is correspondingly low and is of insufficient magnitude to produce the vibrations from which the "presystolic" murmur develops.

When the entire leaflet of the mitral valve is inflexible the valve functions as a flat disc, the central portion of the valve cannot be displaced into the atrium, and accordingly the "presystolic" murmur is replaced by a mid-diastolic murmur.

The authors point out that, while these observations serve to define the genesis of the "presystolic" murmur, they do not alter the diagnostic significance of the murmur.

Observation on the Direct Effect of Digoxin on Renal Excretion of Sodium and Water.—The study reported was undertaken to determine if digitalis had a direct renal effect upon the excretion of sodium, potassium, and water apart from any hemodynamic action. The work was carried out on 17 dogs in whom ureteral catheters were put in place through a midline suprapubic incision. Ten-minute urine samples were collected over control periods of one to two hours after which the left kidney was exposed and varying doses of digoxin, placebo, and mercurial diuretics were injected into the left renal artery. The placebo consisted of the vehicle in which the digoxin was dissolved. The dose of digoxin varied from 0.062 mg. to 0.25 mg.

In the five animals receiving the placebo injection, there was no consistent variation in the sodium, potassium, or water excretion from the injected kidney over that of the control kidney.

When digoxin was injected into the renal artery, there was a pronounced natriuresis and diuresis of the injected kidney as compared with the control kidney. There was no consistent correlation between the degree of natriuresis and diuresis suggesting that the two phenomena might be, in part, independent of each other. Potassium excretion on the injected side did not consistently differ from that of the control. Total endogenous creatinine excretion was unaffected by any of the injections made. One of the dogs used in the study was in congestive failure following experimentally produced mitral stenosis. The natriuresis and diuresis from the injected kidney following the administration of digoxin to this animal was as marked as that seen in the normal animals receiving two to four times the dose of digoxin.

Salyrgan-Theophylline or Mercuhydrin produced a sharp increase in sodium, potassium, and water excretion on the affected side. In the ensuing 10 minutes the same response was noted on the control side. Total endogenous creatinine excretion remained unchanged.

From this study the authors conclude that there is a direct renal effect of digoxin with the production of both a natriuresis and diuresis and they speculate that the heart-failure kidney may be more sensitive to this digoxin effect than the normal kidney. It is postulated that at least part of the beneficial effect of digitalis in heart failure may be the result of the direct effect of digitalis on the kidney.

American Journal of Medicine, New York

20, No. 6 (June) 1956

Loud Presystolic Sounds over the Jugular Veins Associated with High Venous Pressure. William Duck.—p. 853.
Congenital Heart Block. Ephraim Donoso, Eugene Braunwald, Sidney Jick, and Arthur Grishman.—p. 869.
Studies in Ammonia Metabolism: I. Ammonia Metabolism and Glutamate Therapy in Hepatic Coma. B. Eiseman, W. Bakewell, and G. Clark.—p. 890.
* The Treatment of Barbiturate Poisoning With or Without Analeptics. James E. Eckenhoff and Willy Dam.—p. 912.
Effect of Intramuscular Heparin on Antibodies in Idiopathic Acquired Hemolytic Anemia. Karl L. Roth and Abraham M. Frumin.—p. 968.

21, No. 1 (July) 1956

The Problem of Chronic Liver Disease in Young Women. A. G. Bearn, H. G. Kunkel, and R. J. Slater.—p. 3.
* Infectious Mononucleosis Hepatitis: A Clinicopathologic Study. Robert S. Nelson and James H. Darragh.—p. 26.
Essential Familial Hypercholesterolemia and Xanthomatosis: Follow-up Study of Twelve Danish Families. Jorgen Piper and Lis Orrild.—p. 34.
Rheumatic Tricuspid Stenosis: A Clinical and Physiologic Study with a Suggested Method of Diagnosis. Attilio Reale, Harry Goldberg, William Likoff, and Clarence Denton.—p. 47.
A Survey of Allergy's Present Position: Classification of Clinical and Pathologic Features of Allergic Disorders. Milton M. Hartman.—p. 85.
Exocrine Pancreatic Secretion: Effects of Pancreatic Disease. David A. Dreiling and Henry D. Janowitz.—p. 98.
Chronic Idiopathic Jaundice: Two Cases Occurring in Siblings, with Histochemical Studies. Gregory G. John and Kenneth P. Knudtson.—p. 138.
Coexisting Histoplasmosis and Tuberculosis of the Alimentary Tract. J. Winthrop Peabody Jr. and Howard A. Buechner.—p. 143.

The Treatment of Barbiturate Poisoning With or Without Analeptics.—This paper stresses the lack of clinical proof of the effectiveness of analeptics in the treatment of barbiturate poisoning. The mortality reported in four recent studies using analeptics averaged 14.0% among 580 patients, whereas in other series in which only supportive therapy was given 4.2% of 1439 patients died. The use of analeptics may increase mortality by raising the cerebral or cardiac oxygen needs of patients who are already hypoxic.

Therapy should be aimed first to maintain adequate respiration and circulation through the use of such measures as suctioning of the respiratory tree, endotracheal tubes, tracheotomy, artificial respiration, oxygen, intravenous fluids, and vasopressor drugs. Subsequently attention may be directed toward gastric lavage and prevention of infection and of urinary retention. The rapidity with which such supportive therapy is instituted and hypoxia relieved, the dose of barbiturate ingested, and the rapidity of absorption of the drug are the chief factors of importance in influencing the outcome in the individual case. Since much of the care of these patients is similar to postanesthetic care, the assistance of a physician-anesthetist is recommended.

Infectious Mononucleosis Hepatitis: A Clinicopathologic Study.—Nineteen young soldiers with infectious mononucleosis, as evidenced by heterophile agglutination titers of 1:224 or greater, were studied by Nelson and Darragh. All had fever, lymphadenopathy, and typical hematologic findings. Only six demonstrated hepatosplenomegaly, whereas six had splenomegaly. Laboratory studies showed moderate to high sulfobromophthalein (Bromsulphalein) retention in 18, and, of 17 tested, 16 patients had positive cephalin flocculations and 8 showed increased thymol turbidity. Serum bilirubin was elevated in five although only one had clinical jaundice.

Liver biopsy was performed on all 19 patients and demonstrated evidence of hepatitis in all but one if the study was done before the fifth week of illness. Likewise in five of the six severer cases, serial biopsies showed clearing of the pathologic changes by the fifth week of illness. In the sixth case symptoms and pathologic evidence of hepatitis persisted for over eight months. Therefore it was concluded treatment should be similar to that given for viral hepatitis.

Three other patients lacked increased heterophile antibody titers but otherwise presented similar symptoms, signs, and laboratory changes including the liver biopsy findings of infiltration of the portal and sinusoidal areas with mononuclear cells and, less frequently, of areas of focal necrosis. It was felt that these cases also represented infectious mononucleosis and should receive similar rest and dietary therapy because of hepatic involvement.

American Journal of Pathology, Ann Arbor, Mich.

32, No. 5 (Sept.-Oct.) 1956

* Multiple Small Arteriovenous Fistulae of the Lungs. Milton R. Hales.—p. 927.
Varicella: Report of Two Fatal Cases with Necropsy, Virus Isolation, and Serologic Studies. William J. Cheatham, Thomas H. Weller, T. F. Dolan Jr., and John C. Dower.—p. 1015.
The Endocrine Significance of Hypothyseal Tumors in Man. Agnes B. Russfield, Leopold Reiner, and Hanna Klaus.—p. 1055.

Multiple Small Arteriovenous Fistulae of the Lungs.—Two cases of multiple, small pulmonary arteriovenous fistulae were studied by the injection-corrosion cast technique. The first case, that of a 17-year-old boy, had been diagnosed clinically as congenital heart disease. From the age of 8 years he suffered from epistaxis and soon developed cyanosis and exertional dyspnea. Clubbing of the digits appeared, and he suffered from episodes of fainting. He died of purulent meningitis. The second case, that of a 30-year-old woman, apparently followed an attack of hepatitis and postnecrotic scarring of the liver. She had cyanosis, polycythemia, and clubbing. Cardiac catheterization and pulmonary function studies indicated extracardiac arteriovenous shunting. Following a long illness, she died during an attack of severe respiratory distress. The lesions were thought to represent examples of hereditary hemorrhagic telangiectasia, Rendu-Osler-Weber disease, rather than the angiomata of pregnancy and cirrhosis.

The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, Springfield, Ill.

76, No. 1 (July) 1956

* Recurrent Pulmonary Hemorrhage with Hemosiderosis: So-Called Idiopathic Pulmonary Hemosiderosis. Andre J. Bruwer, Roger L. J. Kennedy, and Jesse E. Edwards.—p. 98.
* Polycystic Disease of the Kidney in Infants: Nephrograms Following Intravenous Urography. C. L. Hinkel, and L. C. Santini.—p. 153.
Chelation in Contrast Roentgenography with Special Reference to Lead Disodium EDTA. Robert Shapiro.—p. 161.

Recurrent Pulmonary Hemorrhage with Hemosiderosis: So-Called Idiopathic Pulmonary Hemosiderosis.—Forty-three cases of this disease have been reported previously in the literature. Of these the majority develop symptoms before 5 years of age. Of 25 patients who died before age 20, the average duration of symptoms was 2 years. The prognosis is grave, but recovery is not unknown.

The clinical pattern is discussed under two main types: A. The acute type which show dyspnea, cough, weakness, cyanosis, pallor, and not infrequently abdominal pain. Hemoptysis may occur with the first attack or manifest itself later, usually in blood-stained sputum. Physical signs suggest bronchitis or pneumonia. Later clubbing of the fingers, hepatosplenomegaly and anemia are noted. B. The insidious type in which an acute episode may occur, but most episodes are ill-defined exacerbations on the background of a chronic illness.

There are no characteristic findings of a laboratory nature. Macrophages in sputum are common, however.

The radiographic findings are a reflection of the pathologic lung changes and therefore, are associated with frank pulmonary hemorrhages. These are multiple, blotchy, rapidly clearing shadows differing in detail with each episode of bleeding, but of the same general appearance. In association with repeated episodes a reticulostriate pattern ultimately develops in the lung fields. Hilar lymph-node enlargement may occur.

Three cases are reported with radiographs and pathological discussion. The etiology is unknown, but the possibility of a hypersensitivity state is suggested.

Polycystic Disease of the Kidney in Infants: Nephrograms Following Intravenous Urography.—The disease is familiar when it occurs in adults due to classical deformity

produced by large cysts. In infants where such large cysts are not present other characteristics must be recognized.

Generally the disease is divided into two types, the infantile and adult types. A hereditary predisposition is known.

The infantile type has been classified by Potter as follows: A. Those with a normal amount of connective tissues. Here cysts are uniform in type. The kidneys are bilaterally and symmetrically enlarged and is almost always accompanied by cystic disease of the liver. B. Those with an increased amount of connective tissue. Here cysts tend to be more spherical in shape and variable in size. Involvment often assymetrical. Cysts sometimes produce masses beneath the capsule or renal distortion as in the "Adult Type."

The embryogenesis is not entirely clear, but it is genearlly accepted that there is inhibition of the normal differentiation and the tubules are obstructed.

A case is reported. The radiographic findings are of particular interest in this 8-day-old girl. An I. V. pyelogram revealed no contrast material in the calyces, pelves, or ureters, but a slight nephrographic effect was noted in 5 minutes, which became more marked on subsequent films up to 72 hours after injection. The opacified kidneys were very large and slender. Radiolucent streaks and mottled ovoid and round radiolucent shadows from 2-7 mm. were noted. The retrograde showed no obstruction or deformity of calyces or pelves.

The differential diagnosis is between hydronephrosis or bilateral renal tumor.

A discussion of the nephrograms following intravenous urography is given. This case is felt to be an example of intrarenal obstruction.

The persisting nephrographic phenomenon in the absence of urinary-tract obstruction is of specific diagnostic significance, and findings of mottled radial linear radiolucent defects are pathognomonic of this disease.

American Review of Tuberculosis and Pulmonary Diseases, New York

74, No. 3 (Sept.) 1956

* **The Treatment of Carbon Dioxide Narcosis by the Use of an Automatic Positive-Negative Resuscitator.** H. O. Sieker, J. B. Hickam, and W. W. Pryor.—p. 309.

Carbon Monoxide Diffusing Capacity During Steady Exercise: Comparison of Physiologic and Histologic Findings in Patients with Pulmonary Fibroses and Granulomatoses. David W. Cugell, Asher Marks, Marjorie F. Ellicott, Theodore L. Badger, and Edward A. Gaensler.—p. 317.

Correlation of Tomographic and Bronchographic Findings in Apical Bronchiectasis. J. H. Juhl, W. J. Alt, and R. H. Wasserburger.—p. 388.

Allergic (Löffler's) Pneumonitis Occurring During Antituberculous Chemotherapy: Report of Three Cases. DeWitt E. Wold and Daniel W. Zahn.—p. 445.

Use of Reserpine in the Treatment of Mental Patients Who Are Tuberculous. A. Crandell and J. Ma.—p. 457.

C-Reactive Protein in Pulmonary Tuberculosis. J. J. Walsh and others.—p. 464.

Concurrent Administration of Pyridoxine and Isoniazid. O. Wasz-Hockert and others.—p. 471.

A Study of Tuberculin Hypersensitivity in 510 Patients Hospitalized for the Treatment of Active Pulmonary Tuberculosis. S. J. Berte.—p. 474.

74, No. 4 (Oct.) 1956

Diffuse Interstitial Fibrosis of the Lungs (Hamman-Rich Syndrome): A Review with a Report of Three Additional Cases. I. W. B. Grant, B. R. Hillis, and J. Davidson.—p. 485.

Simple Tests of Respiratory Function Using a Direct-Writing Ear Oximeter. C. R. Woolf, R. W. Gunton, and W. Paul.—p. 511.

Beryllium Granulomatosis of the Lungs: A Four-Year Follow-Up of Two Patients. Arthur Schwartz, Sidney D. Harvey, and Daniel J. Stone.—p. 533.

Antituberculous Immunity Induced in Mice by Virulent Primary Infection: Its Inhibition by Chemoprophylaxis. Rene J. Dubos and Werner B. Schaeffer.—p. 541.

* **The Influence of Tetracycline Compounds on the Development of Antibodies in Psittacosis.** K. F. Meyer and B. Eddie.—p. 566.

Some Observations on the Pathology of the Lesions Caused by Isoniazid-Resistant Tubercle Bacilli in the Guinea Pig. H. H. Vink et al.—p. 633.

X-Ray Therapy in the Management of Tuberculous Cervical Lymphadenitis. Joseph N. Aceto.—p. 641.

The Treatment of Carbon Dioxide Narcosis by the Use of an Automatic Positive-Negative Resuscitator.—Carbon dioxide narcosis can occur in persons with disorders which greatly reduce alveolar ventilation. The authors report five cases, demonstrating that an automatic mechanical respirator can be effective, and even lifesaving, in the treatment of severe carbon dioxide narcosis. Use of such an automatic mechanical aid to breathing allows the time necessary for steroids, antimicrobials, and anticongestive therapy to correct the factors which originally initiated the severe carbon dioxide retention.

The Influence of Tetracycline Compounds on the Development of Antibodies in Psittacosis.—Early treatment of patients with history of exposure to birds with psittacosis has made diagnosis by the usual laboratory procedures and physical and roentgenographic evidence more difficult. The authors suggest that diagnosis material (blood and sputum) be collected before treatment is begun. The antibody response in psittacosis may be weak and delayed if the infection is treated with large doses of the tetracycline compounds, so that it is still necessary to study the serologic results well into convalescence. It is suggested that a low dose of tetracycline (1.5 gm. daily) is effective in treatment of the disease but may not influence the antibody titer.

Annals of Internal Medicine, Lancaster, Pa.

44, No. 4 (April) 1956

* Intrahepatic Obstructive Jaundice (Primary Cholestasis), A Clinicopathologic Syndrome of Varied Etiology: A Review with Observations of the Use of Corticotropin as a Diagnostic Tool. Henry C. Johnson, Jr. and John P. Doenges.—p. 589.

* The Fate of Children with Bronchiectasis. Christopher Strang.—p. 630.

Acetyl-Digitoxin (Acylanid): Rapid Digitalization and Maintenance by Oral Administration. Isidor C. Brill, Paul R. Burgner, and Norman A. David.—p. 707.

Probable Infectious Mononucleosis Without Positive Heterophil Agglutination Tests. Sidney Leibowitz.—p. 717.

Case Report: Jaundice Associated with the Administration of Sodium *p*-Aminosalicylic Acid: Review of the Literature and Report of a Case. William E. Bellamy Jr., H. Page Mauck Jr., Gordon R. Hennigar, and Milton Wigod.—p. 764.

Case Report: Miliary Tuberculosis Developing During Prolonged Cortisone Therapy of Systemic Lupus Erythematosus. Harold M. Hill and J. D. Kirshbaum.—p. 781.

Editorial: Phenylpyruvic Oligophrenia.—p. 819.

44, No. 5 (May) 1956

A Medical Appraisal of Transaortic Commissurotomy. Joseph F. Uricchio, Robert Litwak, Clarence Denton, Harry Goldberg, and William Likoff.—p. 844.

* Complications of Infectious Mononucleosis. Jason Ned Smith Jr.—p. 861.

Observations on the Individual Effects of Smoking on the Blood Pressure, Heart Rate, Stroke Volume and Cardiac Output of Healthy Young Adults. Caroline Bedell Thomas, John Laurens Bateman, Evan Florian Lindberg, and Harold J. Bornhold.—p. 874.

The Clinical Significance of Hyperglobulinemia: I. Diagnostic Implications. Alvan R. Feinstein and Robert G. Petersdorf.—p. 899.

The Clinical Significance of Hyperglobulinemia: II. Correlation with Liver Function Tests, Serologic Tests for Syphilis, and Bone Marrow Examinations. Alvan R. Feinstein and Robert G. Petersdorf.—p. 925.

"Platelet" Thrombosis in Leukemia. Kjeld O. Husebye, J. M. Stickney, and Warren A. Bennett.—p. 975.

Single Coronary Artery: Report of Two Cases. E. DuBose Dent Jr. and Russell S. Fisher.—p. 1024.

Editorial: The Role of Ammonia in Clinical Syndromes.—p. 1037.

Intrahepatic Obstructive Jaundice (Primary Cholestasis), A Clinicopathologic Syndrome of Varied Etiology: A Review with Observations of the Use of Corticotropin as a Diagnostic Tool.—In some cases of viral hepatitis a peculiar laboratory and histologic picture is seen which is very similar to that in jaundice due to arsphenamine, methyltestosterone, and chlorpromazine administration. Clinically there is not much difference from ordinary cases except that pruritus, prolonged jaundice, and splenomegaly are more common; whereas fever, marked debility, distaste for cigarettes, and hepatomegaly are less prominent. The usual laboratory tests fail to show evidence of hepatocellular disease but resemble the findings in extrahepatic biliary obstruction, although sometimes elevated urine urobilinogen very early in the disease, reduction in cholesterol ester ratio, elevated serum globulin, or reduced serum cholinesterase may reveal cellular dysfunction. Exploratory operations do not demonstrate obstruction of the biliary tree, and biopsies show bile stasis in intralobular canaliculi, a variable amount of inflammation in the portal triads, and only mild focal degenerative changes in liver cells without extensive degeneration, necrosis, or regeneration. There is some evidence that primary biliary cirrhosis may ensue months or years after recovery.

All measures short of laparatomy may not distinguish this syndrome from extrahepatic obstructive jaundice. Two cases were observed in young soldiers in whom treatment with ACTH produced rapid, dramatic relief of obstruction, and other authors have since observed the same effect in six cases. A trial of steroid hormones therefore seems to provide a safer diagnostic method than exploratory surgery as well as a potentially useful form of treatment. Their effect in cases of nonviral etiology has not yet been assessed, however.

The Fate of Children with Bronchiectasis.—Two hundred nine cases referred to a thoracic surgical unit in Newcastle upon Tyne, England, between 1935 and 1948 with bronchiectasis beginning in infancy or childhood were followed for 2 to 15 years. Many were seen before the widespread use of antibiotics and multiple segmental resection. In 38% symptoms dated from the first year of life and in 75% from the first five years. Almost all were believed to have begun after some acute respiratory disease such as pneumonitis, pertussis, measles, bronchitis, and others. There was a high prevalence of sinusitis and pathological tonsils and adenoids in the group.

Common radiologic findings were linear densities or increased bronchovascular markings, atelectasis, normal film (12%), pneumonitis, or cystic changes. Bronchograms were done in 204 cases and bronchoscopy in 190.

Operation was done in 163 cases (48 pneumonectomies and 115 lobectomies) of which 29% were cured, 34% greatly improved, 12% slightly improved, 8% not improved, and 2% worse; the mortality was 15%. The postoperative prognosis is not adversely affected by the severity of the preoperative symptoms except for asthmatic symptoms. Medical treatment alone (postural drainage, expansion breathing) was used in 46 cases in this series and 15 cases in another series because the disease was too slight or too severe for surgery or because operation was refused. In 23 cases where operation was refused, 1 was cured, 5 were greatly improved, 5 slightly improved, and 8 unimproved; 4 died. Cases of localized cylindric bronchiectasis with mild symptoms do very well on medical therapy, whereas patients with fetid sputum, frequent febrile episodes, copious sputum, or clubbed fingers have a poor prognosis. The treatment of choice is extirpation of the diseased area whenever possible.

Complications of Infectious Mononucleosis.—Although relatively uncommon, the possible complications of infectious mononucleosis are various and important because of the difficulty in diagnosis which they almost always occasion. In severe cases mononuclear and lymphatic infiltration may be seen in the liver, central nervous system, lungs, heart, and kidneys as well as the lymph nodes and spleen.

At least 64 cases with severe neurologic complications have been reported, including serous meningitis (meningismus), meningitis, meningoencephalitis, encephalitis, acute polyneuritis or Guillain-Barré syndrome, and peripheral neuropathy. When neurological symptoms and signs precede the more usual manifestations of the disease, difficult diagnostic problems may arise. Grand mal seizures, coma, Cheyne-Stokes respiration, hemiplegia, papilledema, and sometimes residual damage have been reported in cases with encephalitis. Fatality is most frequently seen in the polyneuritis group, having occurred in 4 out of 18 such cases.

Spontaneous rupture of the spleen has been reported in at least 21 patients, with 7 deaths. Some degree of liver-cell damage is believed to be present in nearly all cases, and hepatitis was severe enough to produce jaundice in 6.6% of the patients in one series. Hemoyltic anemia, thought to be due to production of autohemolysins and autoagglutinins by the enlarged spleen, has been reported 16 times. Thrombocytopenic purpura has been described in 16 case reports also. Pulmonary complications are pleural effusion, bronchopneumonia, or pneumonia. Cardiac manifestations found in the literature are nonspecific electrocardiographic changes, autopsy evidence of myocarditis, and a clinical picture of acute pericarditis. Acute abdominal symptoms may be produced by enlarged mesenteric lymph nodes. Nephritis is transient and characterized by hematuria (6% incidence in one group of cases of infectious mononucleosis), white blood cells in the urine, and less often albumin and casts. Oculomotor palsies, papilledema, and conjunctivitis have been found in the eyes. Skin rashes occur in 7.6% of cases according to one report, and they may be of any type.

Archiv für Kinderheilkunde, Stuttgart

152, No. 2, 1956

* Acute Thyroid Poisoning in a Girl, One Year Old, with Mild Hypothyroidism: Treatment with Hydergin and Glucose. T. E. Peltonen and E. M. Ekman.

The Hematological Reaction of Small Doses of Vitamin B_{12} in Pernicious Anemia of the Infant. G. B. Burgio, G. Russo, and F. Lo Jacono.

The Provocation of Typical Pertussis Attacks by Intravenous Injections of Lobelin. F. Hansen and A. Dortmann.

Serum Cholesterol in Measles. A. Solé.

Vitamin Contents of Food Articles (Vitamin D_3). E. Mueller.

152, No. 3, 1956

* Functional Gastroesophageal Incompetence and Diaphragmatic Hernia. F. Rehbein.
On Characteristic Influences of Development of Leucocytes. W. Dietz.
Clinical Experiences on Otological Complications in Whooping Cough. B. Bollobas.
The Treatment of Typhoid Fever With Cortisone and Chloromycetine. K. Choremis, Th. Athanasiadis, Ch. Wonat, D. Zoumboulakis, and K. Kiosoglou.
On the Influence of Sol-Baths on the Organism. U. Gruninger.
* Duodenal Stenosis by Annular Pancreas. W. V. Ekesparre.
* Subarachnoid Hemorrhage in Infancy. W. Schneidt.

153, No. 1/4, 1956

On the Significance of the White Blood Count in Typhoid and Paratyphoid Fever in Children. E. Lorenz.
Nutritional Chylomicronaemia in Healthy Infants. J. Jochims.
Electroencephalogram in Psychomotoric Seizures of Children. R. Garsche.
Salt and Water Treatment in Infants and Children. W. Droese and Stolley.
"Tapeto-Cerebral" Degeneration. Th. Schoenfelder.
Clinical and Epidemiological Evaluation of Complement Reaction in Poliomyelitis. W. Keller and O. Vivell.
Adrenal Functions in Dystrophy. H. Zeisel and J. Stroeder.
Embryopathia Thyreotica. J. B. Mayer and A. Hemmer.
Calicopathia as a Special Form of Urinary Tract Infection. E. Zapp.

Acute Thyroid Poisoning in a Girl, One Year Old, with Mild Hypothyroidism: Treatment with Hydergin and Glucose.—This is a rare case. A one-year-old girl, treated with 0.1 gm. Thyroidin daily for mild hypothyroidism, received from her 2½-year-old sister 1.2 gm., swallowed it, and developed 6 hours later restlessness, tachycardia, mild hypertension, after administration of Hydergin (Sandoz), an ergotartrate product, cyanosis and hypoglycemia that could be successfully corrected by glucose. Though there is a theoretical possibility that Hydergin precipitated the hypoglycemia, it is more likely that the massive dose of thyroid resulted in a disturbed carbohydrate metabolism and mobilized all available glycogen reserves.

The authors, from Finland, consider in the references the foreign literature and emphasize the rarity of such observations.

It is remarkable that neither our pediatric nor pharmacological nor accident prevention books that emphasize the danger of hyperthyroidism in prolonged treatment of hypothyroid conditions ever mention accidental poisoning with thyroid tablets that may not be such a rarity. ("Candies" removed from the purse of an obese woman in a neighboring vacation cabin.)

Functional Gastroesophageal Incompetence and Diaphragmatic Hernia.—The old term "habitual vomiting" loses clinical meaning as an entity, since histology, x-ray, and exploration have eliminated this term that once comprised rumination, aerophagy, nervous constitution, and malformations. In the light of our present knowledge, we must differentiate between 1. hypertonic-atonic dysphagia, as the Germans call it, obviously identical with our chalasia as functional disturbance, and 2. hiatus hernias that may be associated with congenital short esophagus or combined with paraesophageal hernias or, another modification, esophagus of normal length that forms part of the hernia sac. The distinction is of clinical importance, since in the anatomical picture esophagitis, caused by peptic digestion, and strictures form a great risk. The author says that the radiological distinction is possible by patiently performed serial films in ventral, dorsal, and Trendelenburg position that illustrate gastric mucosa in the thoracic stomach. He discusses the normal and pathological conditions of sphincter function of the cardia muscle, the loop effect of the hiatus, and the acute-angled opening of the esophagus in the fundus. He describes the surgical procedures in real hernia and emphasizes the relative frequency of relapses from literature studies. It is interesting to confront his statements with our literature. One of the most comprehensive studies (*Radiology* 64, May, 1955) stresses the fact that contracted esophageal musculature may easily simulate gastric mucosa and a hernia. The British literature reports a high incidence of short esophagus, and Neuhauser feels, probably because the early cases of hernia esophagitis secondarily leads to shortening, that these cases are not adequately recognized.

Duodenal Stenosis by Annular Pancreas.—Annular pancreas is a congenital malformation of the head of the pancreas. It is characterized clinically by an almost invariably completely closed ring that encircles the descending loop of the duodenum. Though the embryogenesis is controversial, the most likely origin rests on a bilateral fusion of the ventral primordia (from the common bile duct) and the dorsal duodenal derivative. The degree of manifestations depends on the severity of compression, which may result in complete obstruction or,

at a later age, lead to inflammatory reactions, such as pancreatitis or icterus. As a rule, the diagnosis is made postmortem; intra vitam one suspects duodenal atresia. Clinically, the signs are identical; however, x-ray (pars superior duodeni dilated, secunda constricted, ascendens collapsed) may suggest the underlying anomaly. Description is given of a case (boy, 3 days) with ectatic stomach, "tobacco-pipe" distended bulbus duodeni. Dissection of the ring was contraindicated because of the risk of pancreatic fistula; duodenojejunostomy was the method of choice and resulted in uneventful postsurgical course.

Subarachnoid Hemorrhage in Infancy.—Description of three cases of subarachnoid hemorrhage in infancy: Case 1 was a 7-month-old boy, admitted with signs of left-sided spastic paresis, convulsions, hematomas of helix, cheek, arm, gluteal region, bloody spinal and suboccipital fluid, retinal hemorrhages, and later xanthochromia of spinal fluid; at the age of 2 years 8 months there were no neurological or mental after-effects. Etiologically either long labor or otitis at 7 months or vascular deficiency was probable. Arteriogram was not performed. Case 2 had similar clinical manifestations; cause was congenital syphilis. Age: 8 months. Case 3 was a 3-weeks-old infant with no evidence of trauma, birth injury, or preceding infection.

The author discusses the relative infrequency of subarachnoid hemorrhage in infancy and early childhood, in contrast to the prevalence in adulthood and the high incidence of subdural hemorrhages in children. He quotes the German pediatric textbooks that partly deny the occurrence in children, party emphasize the difficult diagnosis and the confusing nomenclature (six terms quoted).

It is interesting to confront the German observations with the reports of other countries. The 1920 edition of Griffith (later Mitchell-Nelson) does not mention subarachnoid hemorrhage, the 1945-1956 Pediatric yearbooks do not contain one reference, the recent editions of Mitchell-Nelson discuss the etiology of trauma, infection, blood dyscrasia, and the symptomatology, disregarding age-distribution.

The English literature (*Brit. M. J.* March 17, 1951) summarizes the single observations in infancy and childhood in an excellent symposium and remarks that the relative infrequency is surprising because of the congenital nature of aneurysms of the circulus Willisi, the most important causative factor. This proves that malformations often produce diseases in adulthood, not earlier.

Blood, New York

11, No. 7 (July) 1956

* A Case of Anti-Cellano. Filomena P. Innella, Curtis R. Boyd, and G. B. Stansell.—p. 641.
The Present Status of Treatment of Autoimmune Hemolytic Anemia with ACTH and Cortisone. William Dameshek and Zacharias D. Komninos.—p. 648.

11, No. 8 (Aug.) 1956

Hemostasis in Thrombocytopenic Bleeding Following Infusion of Stored, Frozen Platelets. Edmund Klein, Rudolf Toch, Sidney Farber, Gustave Freeman, and Rosemary Fiorentino.—p. 683.
* Studies on the Specificity of Autoantibodies in Acquired Hemolytic Anemia. Leonard V. Crowley and Bertha A. Bouroncle.—p. 700.
Hageman Factor (HF) Deficiency. Brancha Ramot, Karl Singer, Paul Heller and Hyman J. Zimmerman.—p. 745.
Paroxysmal Nocturnal Hemoglobinuria. A. M. Nussey and D. W. Dawson.—p. 757.

A Case of Anti-Cellano.—Detection of the rare anti-Cellano antibody during antepartum testing of an Rh-negative mother is described. In this case maternal immunization was in all probability stimulated by past transfusions and/or pregnancies. There was passive maternal transfer of antibody to the newborn but no adverse clinical effects were manifest in this infant, who was Cellano negative. The infant had anti-Cellano antibodies in the same titer as that of the mother.

The report is of interest, since the antibody was detected during routine testing for Rh antibodies and emphasizes the usefulness of the Coombs' test in prenatal and pretransfusion hematoimmunologic studies.

Studies on the Specificity of Autoantibodies in Acquired Hemolytic Anemia.—In the past autoantibodies found in autoimmune hemolytic anemia were thought to react with some common antigen possessed by all human erythrocytes unrelated to blood group antigens. More recent studies have shown that in autoimmune hemolytic anemias, antibodies may be formed against specific blood group antigens. The authors of the present study have evaluated the

incidence of specific autoantibody formation in 12 patients with acquired hemolytic anemia. In nine of these patients no detectable specificity could be demonstrated, although the possibility remains that the apparently nonspecific antibody may be directed against a commonly occurring blood group antigen or a mixture of antigens. Three patients demonstrated specific autoantibodies. In two the autoantibody was anti-e. In one patient the autoantibody had the specificity of anti-D and anti-E.

Ashby studies indicated that properly selected blood, lacking the antigens against which the autoantibody is formed, can be transfused successfully in these cases.

An analysis of previously reported cases is presented revealing that as many as 50% of patients with autoimmune hemolytic anemia may form single or multiple specific autoantibodies. These findings are not only of fundamental interest but can be applied to the management of patients with acquired hemolytic anemias.

Bulletin of the Johns Hopkins Hospital, Baltimore

99, No. 3 (Sept.) 1956

Studies in Neuromuscular Function:
I. Introduction and Methods. David Grob et al.—p. 115.
II. Effects of Nerve Stimulation in Normal Subjects and in Patients with Myasthenia Gravis. Richard J. Johns et al.—p. 125.
III. Stimulating and Depressant Effects of Acetylcholine and Choline in Normal Subjects. David Grob et al.—p. 136.
IV. Stimulating and Depressant Effects of Acetycholine and Choline in Patients with Myasthenia Gravis, and Their Relationship to the Defect in Neuromuscular Transmission. David Grob et al.—p. 153.

99, No. 4 (Oct.) 1956

Studies in Neuromuscular Function:
V. Effects of Anticholinesterase Compounds, *d*-Tubocurarine, and Decamethonium in Normal Subjects. David Grob et al.—p. 195;
VI. Effects of Anticholinesterase Compounds, *d*-Tubocurarine, and Decamethonium in Patients with Myasthenia Gravis. David Grob et al.—p. 219.
* Methylcellulose as a Wetting Agent in Blood Clot. Morris Rosenfeld.—p. 239.

Methylcellulose as a Wetting Agent in Blood Clot.—The author observed the effects of a number of colloids, including methylcellulose, gelatin, dextran, and carboxymethylcellulose, on the alteration of the clot characteristics of plasma. Of the materials tested, methylcellulose stood out uniquely as a wetting agent. The clot surface takes on hydrophilic properties in contrast to the normal hydrophobic character, and the clot characteristics are altered in a direction that might be favorable for hemostasis. The possible mechanisms whereby methylcellulose has this property are discussed. The author has not studied, but makes the inference of, the possible clinical value of methylcellulose in favorably influencing clot structure.

Canadian Medical Association Journal, Montreal

75, No. 4 (Aug. 15) 1956

Kurtin's Surgical Planing Procedure: A Review of Experiences with Special Reference to Post-Acne Scarring. A. A. Small.—p. 279.

75, No. 5 (Sept. 1) 1956

* Birth Injury or Artefact? S. Mercer.—p. 421.

75, No. 6 (Sept. 15) 1956

* An Evaluation of Infant Resuscitation. O. Schmidt, M. McLandress, and L. Cruickshank.—p. 503.
* Epidermolysis Bullosa of the Newborn. M. Rosset.—p. 507.

75, No. 7 (Oct. 1) 1956

Primary Agammaglobulinemia as a Cause of Repeated Infection in Childhood. C. Sorensen and C. N. Partington.—p. 579.
Studies in Stillbirths and Neonatal Deaths in Winnipeg: I. Objectives and Plan of Organization. E. J. N. Briggs, A. J. D. DePape, Georgina Hogg, J. R. Mitchell, and H. Medovy.—p. 586.

75, No. 8 (Oct. 15) 1956

* Tuberculous Meningitis: Combined Corticosteroid and Antimicrobial Therapy. S. J. Shane, S. E. Copp, and T. K. Krzyski.—p. 631.
* Observations on the Etiology of Acute Laryngotracheobronchitis, Toronto, 1953-1954. E. A. Morgan, J. A. Turner, A. J. Rhodes, Ann M. Peach, Elizabeth Zaiman, and Darline Duncan.—p. 638.

Birth Injury or Artefact?—The author reports and illustrates a stillborn child whose spinal cord was found to be completely interrupted. The baby was premature and was delivered about eight hours after the mother had a profuse vaginal hemorrhage. Instruments were not used.

Three possible causes of the cord abnormality are discussed: (a) artefact, (b) congenital malformation, and (c) birth injury. Artefact appears to be ruled out as does congenital abnormality, and the author concludes that the lesion was the result of birth injury.

An Evaluation of Infant Resuscitation.—This is a report of the results of a questionnaire answered by 61 hospitals with an average of 85.6 bassinets and an average of 3692 yearly births. Many types of mechanical resuscitators were used, and no machine was considered satisfactory. Sixty per cent of the hospitals had definite schemes for resuscitation, and the majority used apnea lasting 1-3 minutes as the indication for active resuscitation procedures.

No perfect classification of asphyxia exists, but 57% of the hospitals were satisfied with the methods and classification in use. In 70% of the hospitals intubation was done to get a good oxygen supply to the baby.

The answers to the questionnaire are tabulated.

Epidermolysis Bullosa of the Newborn.—A case report is given with a good discussion of the condition. Three types exist. 1. Simplex: hereditary transmission dominant. No effect on general condition and condition may be self-limited. 2. Dystrophic: recessively inherited with hemorrhage, scarring, atrophy, pigmentation, degeneration of nails, deformities of teeth, osteoporosis, and atrophy of parts of skeleton. 3. Letalis: rare type, recessive transmission with congenital and very marked skin changes, atrophy of skeleton and malignant course leading to death usually before 3 months of age.

There is a discussion of etiology and the case reported is of the letalis type, successfully treated with cortisone and ACTH. The child has had 5580 gm. cortisone, 4400 gm. hydrocortone and 1200 gm. duracton in the 22 months of her life and is maintained in hospital on 5 mg. ACTH once weekly.

Tuberculous Meningitis: Combined Corticosteroid and Antimicrobial Therapy.—Thirty patients with tuberculous meningitis were treated with intramuscular streptomycin, PAS, and cortisone, with or without isoniazid. Twenty-five of the patients (83.3%) recovered completely. If three children who died because of (a) cerebral infarction and (b) treatment begun in the very late stages are omitted, the recovery rate becomes 92.6%. The authors state that their study was of necessity carried out without controls. There is evidence that the corticosteroid-antimicrobial regimen in tuberculous meningitis has advantages over antimicrobial therapy alone, even when such therapy includes isoniazid.

Observations on the Etiology of Acute Laryngotracheobronchitis, Toronto, 1953-1954.—Clinical and bacteriological findings in 70 cases of acute laryngotracheobronchitis are reported. Bacteriological studies indicated no constant pattern of organisms. Diphtheria bacilli were not found and only one case had Hemophilus influenzae, type B. Five agents, cytopathologic for human embryo lung, and trypsinized monkey kidney cells were isolated—suggesting viral agents as being etiologic. In later work cytopathogenic agents have been isolated from 10 of 15 cases seen in 1955 at the Hospital for Sick Children, Toronto.

La clinica pediatrica, Bologna

38, No. 3 (March) 1956

Two Cases of Neuroblastoma. V. Migliori.—p. 166.
* Electroencephalography in Infants with Hypothyroidism. G. B. Cavazzutti and E. Lanzoni.—p. 179.
A Case of Probable Congenital Tuberculosis. F. Tescola and D. Gobesso.—p. 191.
* Congenital Occlusion of the Nasopharynx of a Newborn Infant. A. Vianello and G. Golfieri.—p. 205.
Pneumocystosis. M. Malessi.—p. 217.
Studies on the Absorption of Penicillin Administered Orally. M. P. Prodi.—p. 223.

Electroencephalography in Infants with Hypothyroidism.—Encephalography was found to contribute to determining the correct dosage of the medication given to infants with hypothyroidism.

Congenital Occlusion of the Nasopharynx of a Newborn Infant.—A baby was born with a complete osteocartilaginous occlusion of the nasopharynx. An immediate differential diagnosis was imperative, since the child tended to go into spells of cyanosis and stoppage of breathing. It was apparent that the child's mouth must be kept continually open. This was accomplished by a rubber catheter with a metal rod inside of it; this was placed in the child's mouth and held in place by cords, much like the bit of a horses bridle. Only after 47 days was the child's nutritional and physical condition such as to permit the surgical opening of the nasal passages.

Endocrinology, Springfield, Ill.

58, No. 1 (July) 1956

* Changes in Extracellular Fluid Levels of Calcium, Phosphate and Citrate Ions in Nephrectomized Rats Following Parathyroidectomy. Roy V. Talmage and J. R. Elliott.—p. 27.
* Inguinal Hernias in Female Mice Treated with Androgens or Bearing Grafts of Testes. John C. Bjorn and W. U. Gardner.—p. 48.
* Effect of Antigonadotrophic Serum on Recent Intrasplenic Ovarian Implants of Castrate Mice. Charles A. Ely.—p. 83.

59, No. 2 (Aug.) 1956

* Anerobic Glycolysis of Human Prostatic Adenoma: In Vitro Inhibition by Estrogen and by Androgen and Estrogen. D. F. McDonald and M. J. Latta.—p. 159.
* Effects of Stress on Serum C^{14} Levels in Rats Following Administration of Hydrocortisone-4-C^{14} and Corticosterone-4-C^{14}. Frank Ulrich and C. N. H. Long.—p. 170.
* Parathyroid Function and the Plasma Citric Acid and Calcium Response to Nephrectomy. Joseph R. Elliott and Smith Freeman.—p. 181.
* The Influence of Age on the Development of Adrenal-Regeneration Hypertension. Floyd R. Skelton and James Guillebeau.—p. 201.
* Interrelations Between Thyroxin and Adrenalin in the Regulation of Oxygen Consumption in the Albino Rat. Heidi Eartly Swanson.—p. 217.

Changes in Extracellular Fluid Levels of Calcium, Phosphate and Citrate Ions in Nephrectomized Rats Following Parathyroidectomy.—Much of the recent interest in parathyroid physiology has pertained to its extrarenal function. Numerous reports have shown that serum calcium changes could be produced in nephrectomized animals both by parathyroidectomy and the administration of parathyroid extract.

The experiments here reported were carried out using nephrectomized rats maintained by peritoneal lavage, and the results show that the extrarenal influences of the parathyroid hormone are realized in equally as short a time as are the renal effects and that the changes produced in the extracellular concentrations of calcium, phosphate, and citrate ions are all of approximately equal magnitude and in the same direction. These studies are in support of the thesis that the parathyroids maintain a constant serum level for calcium by making available calcium and phosphate from the bone while simultaneously raising the renal threshold for calcium and lowering that for phosphate.

Inguinal Hernias in Female Mice Treated with Androgens or Bearing Grafts of Testes.—Hernias developed in mice when the hormonal environment was manipulated in a number of ways, presumably by increasing the levels of androgen.

News and Comment

GENERAL NEWS

Heart Association Issues Revised Statement on Prevention of Rheumatic Fever.—Revisions of its recommendations for prevention of first and repeat attacks of rheumatic fever are incorporated in a new edition of the American Heart Association's statement on "Prevention of Rheumatic Fever and Bacterial Endocarditis Through Control of Streptococcal Infections." The revised statement appears in the December issue of *Modern Concepts of Cardiovascular Disease*, the Association's monthly medical bulletin.

This is the second revision of the statement, prepared by the Association's Committee on Prevention to keep pace with the progressively growing body of knowledge and experience in this field. The Committee points out that no recommendations can be considered final at this time. "Revisions and changes," it declares, "will be made as new knowledge may indicate."

Following are the principal changes in the recommendations:

1. Greater emphasis is placed on the value of throat cultures in diagnosing streptococcal infections, with a view to stimulating an increased use of cultures, particularly when clinical manifestations alone are inconclusive.

2. A more qualified statement is made on the duration of prophylaxis. The Committee reaffirms its view that continuous prophylaxis should be maintained indefinitely for known rheumatic subjects, but recognizes that some physicians may wish to make exceptions in certain of their adult patients, particularly those without heart disease who have had no rheumatic attacks for many years.

3. Monthly injection of 1,200,000 units of benzathine penicillin G intramuscularly is now listed first among prophylactic methods. The Committee also indicates that it is preferable, if oral penicillin is chosen as the method of prophylaxis, to prescribe 200,000-250,000 units twice daily, rather than once, providing an additional safeguard against breakthroughs which have been reported with the smaller dosage.

Also revised in the statement are the recommended dosages for prophylaxis against bacterial endocarditis in patients with rheumatic or congenital heart disease who are obliged to undergo such surgical procedures as dental extractions, tonsillectomies, etc. Emphasizing that the dosage regimens used for long-term prophylaxis of streptococcal infections are inadequate for this purpose, the Committee recommends that high blood levels of penicillin be maintained for several days (rather than, as previously stated, on the day of operation alone) to prevent organisms from lodging in the heart valves during the period of transient bacteremia.

In general, the combined oral and parenteral route of administration is preferred, as follows: Oral penicillin (200,000-250,000 units four times a day) for the two days before and the two days after surgery; the same dosage of oral penicillin on the day of surgery plus 600,000 units of aqueous penicillin with 600,000 units of procaine penicillin shortly before operation. Alternative recommendations are included for situations in which injection is not feasible or penicillin is contraindicated.

In addition to its publication in the December issue of *Modern Concepts of Cardiovascular Disease* the statement will also appear in the January issue of *Circulation*, the Association's journal of clinical cardiology. An outline of a recommended method for culturing beta-hemolytic streptococci from the throat is also being made available by the Association and may be obtained from local Heart Associations or the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

Guide for Parents of Children with Rheumatic Fever.—A new booklet directed especially to parents whose child has rheumatic fever has been added to the publications on this subject now available from the American Heart Association and from affiliated Heart Associations.

The booklet, "If Your Child Has Rheumatic Fever," is an adaptation of a publication issued by the Children's Bureau of the United States Department of Health, Education and Welfare. It provides useful information for reinforcing the physician's advice. The Heart Association points out that physicians may wish to distribute the booklet to parents of children they are treating. It will also be of interest to social workers and public health nurses who are required to interpret the physician's instructions to parents.

PERSONAL

Dr. Wegman Named Secretary General of Pan American Sanitary Bureau.—Appointment of Dr. Myron E. Wegman of the U. S. A. as Secretary General of the Pan American Sanitary Bureau, Regional Office of the World Health Organization, has been announced by Dr. Fred L. Soper, Director of the Bureau.

In accordance with constitutional requirements, the appointment received the prior approval of the Organization's seven-member Executive Committee which represents the 21 American Republics, Members of the Pan American Sanitary Organization. The Committee includes representatives of Bolivia, Colombia, Cuba, Guatemala, Nicaragua, Paraguay, and Peru.

In the position of Secretary General, Dr. Wegman will be the Bureau's chief planning officer, responsible for coordinating the program planning of the Organization in the light of the health needs of the member countries. Since 1952 Dr. Wegman has been Chief of the Bureau's Division of Education and Training, working with medical schools, public health schools, and other educational institutions, which has brought him into close association with all the governments and public health administrations in the Americas. He has recently conducted seminars on preventive medicine in which all medical schools in Latin America participated and is now completing a comprehensive survey of pediatric education throughout the Continent.

Prior to joining the staff of the Bureau Dr. Wegman was professor and head of the Department of Pediatrics at Louisiana State University Medical School, and Pediatrician-in-Chief of the Louisiana State University Pediatric Service at Charity Hospital in New Orleans.

ANNOUNCEMENTS

International Exhibition of Medical Arts.—The Third International Exhibition of Medical Arts, sponsored by the *Minerva Medica* Press Group and the Italian Medical Association (A. M. I.), will be held at the Palace of Exhibitions in the Valentino Park, Turin, from June 1 to 9, 1957. All the latest achievements in the fields of medicine, surgery, and hygiene will be presented in one vast display under their various scientific, technical, and practical aspects. During the same period, there will be several Conferences on Medicine, Surgery, and Pharmaceutical technique; and a Scientific Exhibition and the Third International Festival of the scientific Medical Film will also be held. When last held in Turin, in 1951 and 1954, these exhibitions and conferences were an outstanding success, partly because of the striking display to be seen at the International Exhibition of Medical Arts, but also because of the importance of the scientific Conferences, which were attended by thousands of doctors, surgeons, and specialists from all quarters. A still greater number of medical men from all parts of the world is expected to take part in the next Meetings. Turin has been selected for the Exhibition and the Conferences, not only because it has a splendid tradition in the fields of medicine and surgery, but also because it possesses one of the finest exhibition buildings in the world, The Palace of Exhibitions in the Valentino Park.

Books

BOOK REVIEWS

Allergy in Childhood. By Jerome Glaser. Price, not given. Pp. 529, with 40 illustrations. Charles C Thomas, Publisher, Springfield, Ill., 1956.

This is an excellent book which fills a long-standing need. Dr. Glaser has written many articles on various phases of pediatric allergy that have done much to clarify this subject. Now he has produced a complete text covering all of the phases of pediatric allergy. Up to date discussions are given regarding all phasis of diagnosis and therapy including chapters on antihistamines and steroids. The clinical diagnosis is completely discussed with careful differential diagnostic procedures. The techniques of skin testing are described in detail and further amplified by photographs. One of the outstanding features of the book is the collection of color photographs of various allergic skin conditions. In summary, this text is recommended without reservation to all who treat children and come into contact with this common problem of the allergic child.

Of Water, Salt and Life. By Lakeside Laboratories, Inc. Price, $7.50. Pp. 72, with 31 illustrations. Lakeside Laboratories, Inc., Milwaukee 1, Wis., 1956.

An atlas of fluid and electrolyte balance, this book describes normal and pathological conditions by the use of 31 colored plates, each accompanied by brief explanatory remarks. Three graphic devices are employed in this presentation: the first is a highly diagrammatic but effective representation of the fluid compartments of the body; the second is a "three-dimensional" adaption of the familiar Gamble diagram with the various ions depicted in brilliant hues; thirdly, a diagram of the nephron is variously employed to illustrate the role of the kidney in fluid and electrolyte balance. The book is divided into four sections: basic physiologic considerations; pharmacology of diuresis and antidiuresis; disorders of fluid and electrolyte balance, and fluid and electrolyte replacement therapy. Included in the discussion of disorders of fluid and electrolytes are congestive heart failure, hepatic cirrhosis, acute nephritis, nephrosis, lower nephron nephrosis, gastrointestinal disorders, iatrogenic salt depletion, heat exhaustion, and burns and shock.

The plates are ingeniously and accurately designed and are expertly reproduced. The explanatory remarks are written in a straight forward manner making an understanding of the plates relatively simple. As is stated in the introduction, such a book must inevitably include statements concerning controversial issues, which are not acceptable to all authorities in the field, and cannot include a great variety of opinions on these matters. The primary value of this book would appear to be as an aid in teaching whereby the student is given a visual concept of the relationships of fluid and electrolyte balance.

Cerebral Palsy—Advances in Understanding and Care. By Viola Cardwell. Price, $5. Pp. 625, with 81 illustrations. Association for the Aid of Crippled Children, Room 713, 1790 Broadway, New York 19, 1956.

This reference and textbook in the field of cerebral palsy is perhaps, to date, one of the most complete and finest interpretations of the problem as it is seen by many persons working in this field. This is not the compilation of facts of one person but is the result of thought and consideration of many advisors in numerous special fields, each person's contribution being quite accurate both scientifically and insofar as the less common aspects of cerebral palsy are seen by the practicing physician. It contains the various different attitudes and considerations necessary for the proper management of the entire team approach to cerebral palsy. In addition to giving the practicing physician or person interested the essential facts as they are known today, complete lists of therapeutic equipment, films, and a very, very complete bibliography are available. It is recommended that all persons interested in the problems of the cerebral palsied patient make use of this most excellent text of advances in understanding and care of cerebral palsy.

Neurology and Psychiatry in Childhood: Proceedings of the Association, December 1954, New York, N. Y. Edited by Rustin McIntosh and Clarence C. Hare. Price, not given. Pp. 504, with several illustrations. The Williams & Wilkins Company, Baltimore, 1954.

The 1954 research publication by The Association for Research in Nervous and Mental Disease has produced an outstanding text of the commonest and most typical problems in neurology and psychiatry in children. It is preceded in many instances by basic anatomical information which is of great value to the worker within the field. The adequate evaluations of the discussions that have followed the presentation of these papers have been carefully selected and add considerable value to the text of the preceeding chapters. The information on basic physiology and function of the nervous system is easily read and understandable. The bibliographies are quite complete and add considerable value to the text as a reference book. It is to be noted that some of our most prominent physicians in the field of neurology and psychiatry are well represented, and this text joins some of our greatest reviews of these problems in our present libraries.

Handbook of Pediatric Medical Emergencies. Edition 2. By Adolph G. DeSanctis, with the collaboration of Charles Varga. Price, $6.25. Pp. 389, with 73 illustrations. C. V. Mosby Company, St. Louis, August, 1956.

The second edition of this popular reference book on pediatric emergencies has been expanded to include chapters on Metabolic Emergencies, Accident and Poison Prevention, Genitourinary Emergencies, and Respiratory Paralysis in Poliomyelitis. Much of the original material has been rewritten. The book may be divided into (A) General Sections: 1. performance of procedures; 2. management of pediatric emergencies; 3. treatment of drowning; and (B) Specific Treatment of Poisoning due to a Variety of Substances.

A wealth of valuable information is presented in this book in a succinct and usable manner, and it should be of great value to physicians who deal with children, particularly in smaller hospitals. The material on poisonings is particularly well presented. On the other hand, it would seem that this type of book would be of much less value in the hospital concerned with training pediatric residents and teaching medical students, since the authors must obviously present one particular way of handling situations without a discussion of alternatives. These methods, however effective, are often of considerable variance with those being practiced in a given institution and hence constitute a source for confusion; this particularly applies to the recommendation of drugs and solutions by brand names. With these reservations the book is recommended as a source of valuable and occasionally urgently needed information.

"My child gained faster at that stage . . ."

The physician's function is complicated by the belief of many mothers that "heaviness" is the all-important indicator of physical progress. Obviously, it "cannot be taken as the *only* criterion of health and may be misleading at times. . . ."[1] More important than weight gain, per se, is *physiologic* weight gain.

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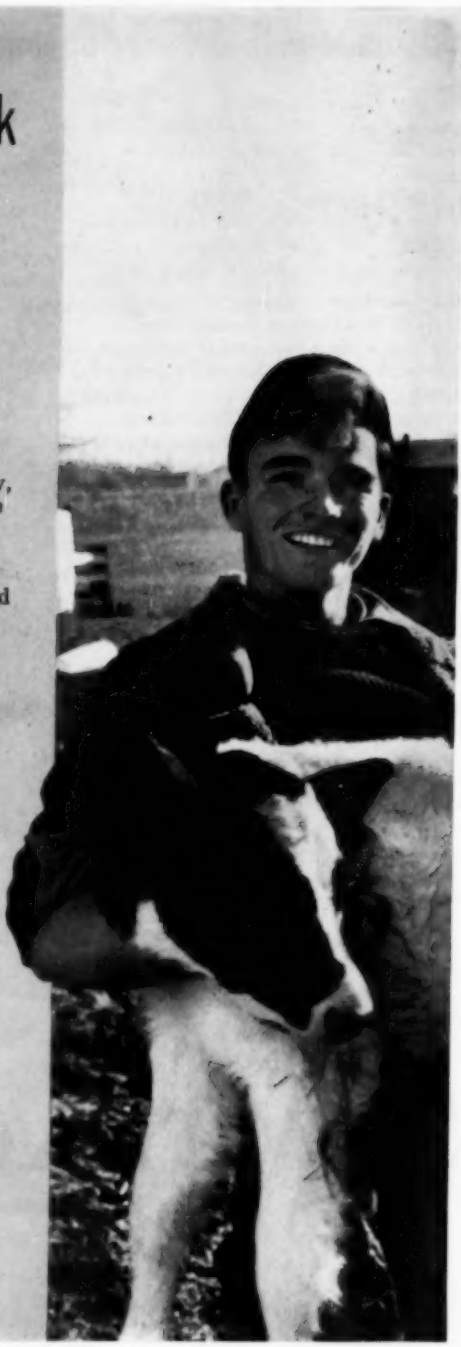

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Enriched Bread makes a nutritionally significant contribution to the joy children find in eating. Every mother knows the happy anticipation with which children reach for a peanut butter sandwich, for a piece of "jelly bread," for a hamburger or hot dog in a toasted roll.

And every mother should know that enriched bread is truly rich in many important nutrients, all of them needed for good nutrition, good nutritional health, and good growth: the vitamins thiamine, riboflavin, and niacin, the minerals calcium and iron, and good quality protein.

Enriched bread is palatable, appetizing, and easy-to-eat... Enriched bread, which was designed fifteen years ago for better national nutrition and improved health, is now praised as one of the most important advancements in public health measures since compulsory pasteurization of milk.

AMERICAN BAKERS ASSOCIATION

20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

For HARD, DRY STOOLS OF
CONSTIPATED BABIES

Borcherdt

MALT SOUP *Extract**

A gentle laxative modifier of milk. One or two tablespoonfuls in the day's formula—or in water for breast fed babies—produce a marked change in the stool.

SAVES DOCTOR'S TIME, TOO!

Fewer phone calls from anxious mothers. Malt Soup Extract is merely added to the formula. Prompt results. Easy for mother to prepare and administer. Does not upset the baby.

*Specially processed non-diastatic malt extract neutralized with potassium carbonate. In 8 oz. and 16 oz. bottles.

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217 N. Wolcott Ave. • Chicago 12, Ill.
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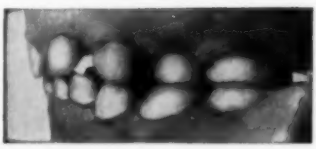
THUMBSUCKING

since infancy caused this 4 year old's malocclusion.



THUM
TRADE MARK

THUM broke the habit and teeth returned to normal position in 9 months.

THUM DISCOURAGES NAIL BITING TOO

GET THUM AT YOUR DRUGGIST OR SURGICAL DEALER.
PRESCRIBED BY PHYSICIANS FOR OVER 20 YEARS.

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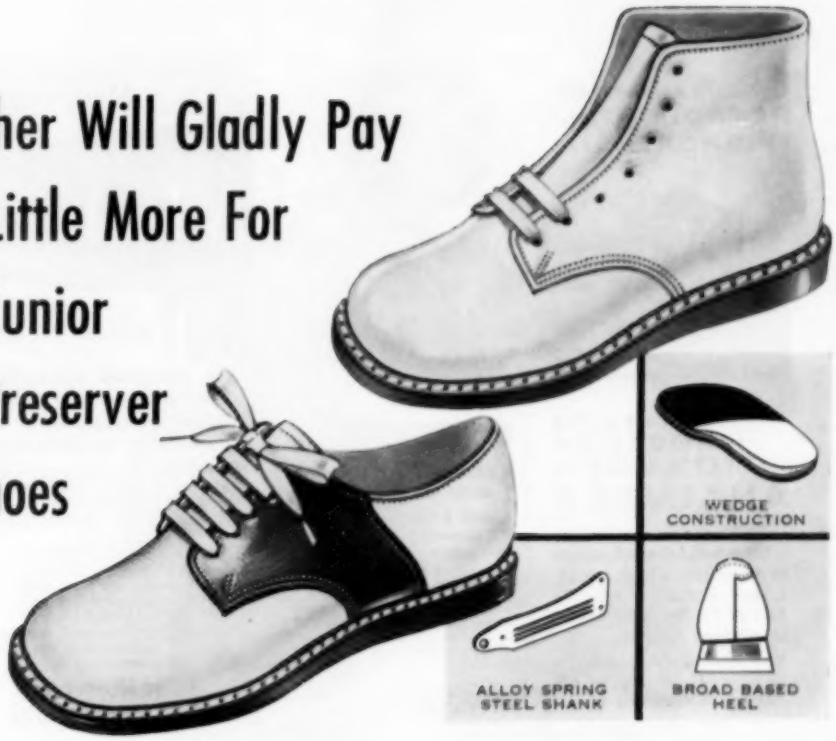


It is true that Selby Junior Arch Preservers cost slightly more than other children's shoes. They cost more because there is no compromise with quality of materials or care of workmanship in their construction. It requires more time and care to make them.

A mother will gladly pay more for Selby Juniors because she knows she can trust their fine craftsmanship. And many doctors recommend Selby Juniors because they admire the exceptional quality of these famous shoes.

The excellence of Selby Junior Arch Preservers is the result of the knowledge and skill acquired in more than three quarters of a century of fine shoemaking. **You can recommend** Selby Juniors for infants and children with complete confidence.

The Shoes, Designed For Children, That Many Doctors Praise

More Than Three Quarters Of A Century Of Fine Shoemaking

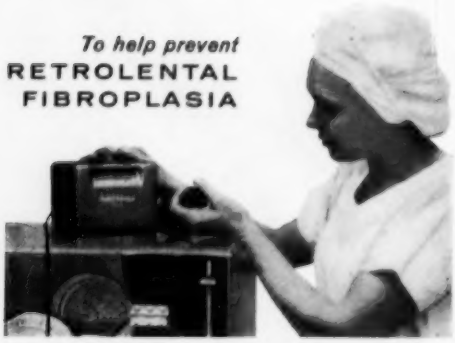
The Selby Shoe Company

Portsmouth, Ohio

Selby
JUNIOR ARCH PRESERVER
Shoes

If Selby Junior Arch Preservers are not available in your city, please write directly to us.

To help prevent
RETROLENTAL
FIBROPLASIA



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MODEL D2
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*Shwachman, H., Children's Hospital, Boston; The Child in Health and Disease, Grulee and Eley, 2nd Edit.

Butler, A., Harvard Medical School, private communication.

Kagan, B., Ill. Med. Jl. 107; 120, (1955).

Gibbs, G. E., Bradley, J. E., and Minor, J. V., Diagnosis and Treatment of Cystic Fibrosis of the Pancreas. J.A.M.A. 145; 1187 (1951).

Everson, T. C., Grossman, M. I., and Ivy, A. C.: Bulletin of Amer. College of Surgeons, January, 1950.

Write for Literature
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